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RHEUMATIC INFECTION IN CHILDHOOD: INFLUENCE OF TYPE OF ONSET AND CALENDAR YEAR OF ONSET

RACHEL ASH, M.D.
PHILADELPHIA, PA.

IN A PREVIOUS paper[1] a statistical analysis was presented of a group of rheumatic patients who had been under the care of the Children's Hospital during the years 1922-1932, inclusive. The initial year, 1922, was chosen because it marked the time when the clinic for supervision of patients with rheumatic infection or heart disease had been founded by the late Dr. Horace H. Jenks.

The present paper extends this analysis to cover the first fifteen years of the clinic. It is based on a follow-up study of all rheumatic children whose primary manifestation had occurred during the years 1922-1936, inclusive, and who had come under the care of the Children's Hospital, either in the wards or Outpatient Department. Rheumatic infections of all degrees of severity were included. Forty-six children had been admitted to the ward with infection serious enough to result in death before the termination of the first year of the disease. In five instances the duration of the fatal illness had been less than one month. Seventy-eight children had been cared for solely through the Outpatient Department. Of the children discharged from the ward, those unable to afford private medical care had been kept under the supervision of the clinic until their fourteenth year, at which time they were transferred to cardiac clinics for the care of adults. Patients of private physicians were advised to remain under the continuous supervision of their medical advisors.

All children on whom the diagnosis of rheumatic infection had been made were included, irrespective of the presence or absence of clinically recognizable heart disease.

Of the original group of 583 children, 473 (81.1 per cent) were white; 110 (18.9 per cent) were colored; 255 (43.8 per cent) were

From the Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania Medical School.

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males, and 328 (56.2 per cent) were females. One hundred thirty-seven (23.8 per cent) had been under the care of the Children's Hospital prior to the onset of rheumatic infection.

The average age at onset was 6.9 years, with limits varying from 17 months to 12 years. Six children were less than 2 years of age at the time of their primary manifestation, and nineteen, less than 3 years.

In 1939, all children not under current observation were requested to return for examination. Additional information was obtained from the records of other hospitals or private physicians who at some time had been responsible for the care of these patients. As a result of these efforts, 527 (90.4 per cent) were traced. Of those concerning whom no information could be obtained in 1939, twenty-six had been followed previously for periods ranging from three to thirteen years. The course of the disease was thus known over a minimum period of three years and an average period of 9.6 years for 553 rheumatic children. Among these, signs of heart disease had been noted at one time or another in 414 (71.0 per cent), but, because of regression of such signs in some patients, a diagnosis of organic valvular damage had eventually been made in only 355 (64.2 per cent). One hundred forty-six (26.4 per cent) had died; of these, 120 (21.7 per cent) had died of rheumatic infection only; 13 (2.3 per cent) of superimposed bacterial endocarditis; 7 (1.3 per cent) with an associated infection, e.g., pulmonary tuberculosis, diphtheria, pertussis, scarlet fever, lobar pneumonia (three cases); and 6 (1.1 per cent) of unrelated causes (Table I).

TABLE I

TOTAL GROUP: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	564	57.9	7.9	1	514	53.3	11.0
3	553	60.4	13.2	2	473	53.9	13.8
5	501	62.0	16.9	4	405	54.5	11.6
7	413	65.6	22.5	7	308	54.5	11.7
10	280	70.4	29.8	2	199	54.8	7.0
{3 to 17 {Average 9.6	553	64.2	21.7	13	398	52.3	12.0

Nine patients were known to be leading a normal existence, but no information was available as to their cardiac status. At the final examination of the remaining 398 survivors, 208 (52.3 per cent) presented signs of organic valvular disease; in 48 (12 per cent), murmurs were audible which could not be differentiated from those of accidental or functional origin; 142 (35.7 per cent) showed no signs of heart damage. Twenty-two were ill with acute recurrences. Ten were cardiac

invalids. The remaining were leading a normal life, although thirty-seven were slightly limited in their ability to undertake physical exertion. Of the twenty girls who had married, all were doing their own housework. Ten had given birth to fifteen children.

The criteria used for diagnosis were those advocated by the American Heart Association.[2] For the detection of cardiac enlargement, use was made only of the position of the apex beat and the teleroentgenograms. No application was made of the angle of clearance test described by Wilson.[3]

INFLUENCE OF THE TYPE OF ONSET ON PROGNOSIS

Since the course of rheumatic infection is modified by many variable factors, analysis of a heterogenous group over an average period of time may be misleading. In an attempt to obtain further information, the course of the disease as modified by the type of initial infection has been traced over definite periods of time.

In considering the initial infection, antecedent upper respiratory infections, including pharyngitis and tonsillitis, have been ignored, because, in the present state of our knowledge, it does not seem possible to decide whether such infections are coincidental, predisposing, or true primary manifestations.

TYPE OF ONSET

Acute carditis (47 children; 8 per cent).—The diagnosis of primary carditis was made in the presence of a febrile illness of sudden onset, associated with signs of cardiac damage. Sudden primary carditis tended to attack the youngest children, for the average age at onset (5.7 years) was somewhat over a year less than that of the group as a whole (6.9 years). The initial mortality was highest among these children, 30 per cent of whom ran a rapidly fatal course, and 65 per cent of whom were dead at the end of ten years. Regression of signs of heart disease occurred in only two instances (Table II).

TABLE II

ONSET WITH ACUTE CARDITIS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	46	97.8	30.4	0	32	96.9	0
3	45	97.8	42.2	0	26	96.1	0
5	40	95.0	45.0	1	21	90.5	4.8
7	31	96.8	51.6	1	14	92.9	0
10	23	100.0	65.2	1	7	100.0	0

Polyarthritis (314 children; 53.9 per cent).—The diagnosis of acute polyarthritis was made when the initial illness was associated with migratory joint pains, fever, and prostration of a degree sufficient to require rest in bed. The average age at onset (6.6 years) was only slightly less than that of the group as a whole. The incidence of clinically demonstrable heart disease at the onset was 59 per cent. Of the patients whose illness had run a course of ten years, 72 per cent suffered from rheumatic heart disease. Almost 10 per cent of the children were dead at the end of the first year, and 30 per cent, at the end of ten years (Table III). It was, however, among the children with early cardiac damage, the extent of which increased with each recurrence, that death occurred most frequently. In contradistinction, of thirty-four children with an early diagnosis of potential or possible heart disease who had been traced at the end of ten years, only 24 per cent had developed definite heart disease, and death had occurred in only one instance.

TABLE III

ONSET WITH ACUTE POLYARTHRITIS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	301	59.1	9.6	0	270	53.5	12.6
3	297	63.6	16.1	0	246	56.1	13.0
5	264	65.5	19.7	1	218	54.5	10.5
7	224	67.0	25.0	4	163	54.6	11.6
10	151	72.4	30.4	4	100	59.0	7.0

Chorea (116 children; 19.8 per cent).—The diagnosis of Sydenham's chorea was made only in the presence of the triad of emotionalism, hypotonia of muscles, and gross incoordinate movements of an abnormal nature. Chorea tended to attack the older children; the average age at onset (8.0 years) was approximately one year greater than that of the group as a whole. In itself, it was a relatively benign manifestation. At the end of the first year, 22 per cent had valvular heart dis-

TABLE IV

ONSET WITH CHOREA: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	113	21.6	2.7	0	108	19.5	5.5
3	110	31.9	2.8	0	106	30.2	11.3
5	101	38.6	3.9	1	94	37.2	11.7
7	81	44.0	9.9	0	71	38.0	14.1
10	56	41.0	16.1	1	46	39.1	6.5

ease, and 2.7 per cent had died. After ten years, 41 per cent suffered from rheumatic heart disease, and 16 per cent were dead (Table IV). All deaths had resulted from carditis, which had made its appearance subsequent to onset. In only nine of the forty-six cases of rheumatic heart disease had the latter developed without a known history of arthritis, carditis, or myalgia. The diastolic rumble of mitral stenosis became suddenly audible in two patients whose only previous rheumatic manifestation had been chorea.

Myalgia and joint pains (53 children; 9.6 per cent).—Children with complaints of myalgia and joint pains not severe enough to force them to go to bed were considered rheumatic if such pains were associated with signs of infection, such as increased sedimentation rate, leucocytosis, or slight fever. Many were brothers or sisters of patients who had suffered from more acute manifestations. These children tended to be older than the run of the group; the average age at onset was 7.5 years. Heart disease at onset was noted in 47 per cent, and at the end of ten years in 58 per cent, at which time 17 per cent were dead (Table V).

TABLE V

ONSET WITH MYALGIA AND JOINT PAINS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	55	47.3	0	0	55	47.3	25.4
3	53	41.5	3.7	0	50	38.0	30.0
5	50	40.0	8.0	0	45	33.3	20.0
7	35	54.3	8.6	0	31	48.4	33.3
10	24	58.3	17.0	0	20	50.0	15.0

Insidious Carditis (48 children; 8.7 per cent).—A diagnosis of insidious carditis was made when valvular lesions characteristic of rheumatic heart disease were found on the first examination of a child with no known history of illness or with a history of scarcely recognized,

TABLE VI

ONSET WITH INSIDIOUS CARDITIS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEUMATIC %	BACTERIAL ENDOCARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	49	100	0	0	48	95.8	4.2
3	48	93.6	2.1	2	44	95.4	4.6
5	46	89.1	14.6	0	37	89.2	10.8
7	39	92.3	25.6	1	26	88.4	11.6
10	26	96.1	37.0	0	16	93.7	6.3

mild symptoms of ill-health. When no definite information as to initial illness could be elicited, the time of the first examination was taken as the time of onset. The average age of this group when the state of ill-health was first noted was 7.0 years. At the end of ten years 37 per cent were dead (Table VI).

INFLUENCE OF CALENDAR YEAR OF ONSET ON PROGNOSIS

The previous follow-up study of patients who were seen prior to 1932 had presented evidence to indicate a progressive lessening of severity of rheumatic infection. The present analysis shows a continuation of this trend. In each successive five-year period since 1922, there has been a lowering of mortality and of the incidence of obvious cardiac involvement, both in the entire group and among those whose first manifestation was polyarthritis or acute carditis (Fig. 1).

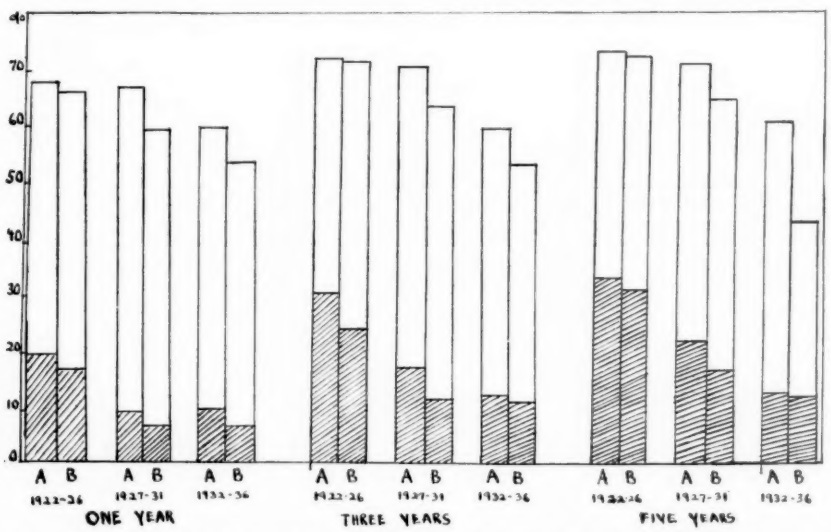

Fig. 1.—Trend toward lessening of severity of rheumatic infection over fifteen-year period. Column *A* indicates the incidence of cardiac involvement in the entire group, with onset of infection during the years noted, and Column *B*, the incidence among those with polyarthritis or carditis at onset. The shaded areas indicate the percentage of deaths due to rheumatic infection.

Various factors have been analyzed in the effort to find out whether this seeming improvement might have been due to a difference in the composition or treatment of the group.

There has been a shift in racial composition during the period of observation; the number of colored children has shown a slow increase, whereas, among the white patients, children of Italian derivation have increased in number (Table VII). Such a change, however, should have influenced the situation for the worse, because the death rate among colored children was 31 per cent, as compared with a death rate of 22 per cent among Italian children and 22.5 per cent among all white children.

TABLE VII

RACIAL COMPOSITION

YEARS OF ONSET	WHITE		BLACK		ITALIAN	HEBREW	NORTH EUROPEAN
	#	%	NO.	%	%	%	%
1922-1926	127	85.8	21	14.2	35.8	12.2	37.8
1927-1931	170	81.7	38	18.3	44.2	6.7	30.8
1932-1936	153	77.3	45	22.7	50.5	5.6	20.4

The distribution of children according to type of onset shows no significant variation within each of these five-year periods. The incidence of cardiac damage of sufficient severity to present obvious clinical signs has, however, shown a progressive decline among children whose first manifestations were those involving the joints (Table VIII).

TABLE VIII

DISTRIBUTION ACCORDING TO TYPE OF ONSET

	1922-26		1927-31		1932-36	
	PER CENT OF TOTAL GROUP	INCIDENCE OF CARDITIS FIRST YEAR	PER CENT TOTAL GR.	INCIDENCE CARDITIS FIRST YR.	PER CENT TOTAL GR.	INCIDENCE CARDITIS FIRST YR.
Polyarthritis or joint pains	63.4	70.2	64.7	64.2	62.2	52.0
Chorea	18.2	22.2	18.8	25.6	21.7	21.4
Carditis, acute or insidious	18.2	100.0	16.4	100.0	16.1	100.0

There has been no consistent decrease in recurrences within the first three years after onset. Among those taken ill in 1922-26, 68 per cent suffered recurrent attacks of polyarthritis, carditis, chorea, or joint and muscle pains of rheumatic origin within three years. Among those attacked during 1926-31, the percentage of recurrences had risen to 75. The year 1929, which fell during this period, had previously revealed itself as a year in which rheumatic manifestations were unduly frequent. The early years of the depression, beginning with 1929, were difficult years for many of the families cared for at the Children's Hospital; there was sudden unemployment at a time when no consistent policy of organized relief had been established. Despite the increase in recurrences, however, the death rate continued to decline. In the third five-year period, recurrences within the first three years had dropped to 56 per cent. In the entire group, 64.3 per cent developed recurrences within three years, and 70.5 per cent within five years. Nine per cent were free from rheumatic manifestations for a period of five years after the original attack, only to develop a flare-up of the disease subsequently.

The policy of the hospital regarding admissions has not changed. To what, then, may we attribute the improvement in the clinical course?

Part, if not all, of this improvement would seem to be due to a spontaneous change in the character of the disease. Hedley[4] has re-

cently brought to our attention the decrease in mortality from heart disease since 1922 among persons between 5 and 24 years of age, a period when rheumatism is the most frequent etiologic factor. In the Middle Atlantic States, the decline in the mean death rate during 1930-36, as compared with 1922-29, was 27.2 per cent, and, in Pennsylvania, 24.5 per cent. At the Children's Hospital the death rate during the first three years among children who were taken ill during 1930-36 was 10.8 per cent, as compared with 18.3 per cent among those taken ill during 1922-29, a decline of 40.9 per cent.

Although there has been no change of policy regarding admissions at the Children's Hospital, it is perhaps significant that within recent years there has been a change in the relative attention paid to the child with the first manifestation of the disease. Prolongation of hospital stay, moreover, has been favored since 1931 by the use of the sedimentation rate of erythrocytes as an indication of the existence of active infection. That slow but definite progress has been made toward the goal of prolonged care for the child when it is first taken ill with rheumatic infection, without regard to the existence of clinically recognizable heart disease, is indicated by the fact that such children have been kept on the wards for increasing periods of time (Table IX).

TABLE IX

DURATION OF HOSPITAL STAY: 189 PATIENTS WITH POLYARTHRITIS OR CARDITIS ADMITTED DURING FIRST YEAR OF RHEUMATIC INFECTION

YEARS OF ONSET	10 OR MORE WEEKS		6 OR MORE WEEKS		4 OR LESS WEEKS		TOTAL NUMBER OF PATIENTS
	NO.	%	NO.	%	NO.	%	
1922-26	9	19.6	19	41.3	26	56.5	46
1927-31	16	24.6	33	50.7	29	44.6	65
1932-36	26	32.5	53	67.9	21	26.9	78

The value of prolonged bed rest in lessening the incidence of noticeable rheumatic heart disease has been demonstrated in London,[5] where, as a result of cooperative effort between school and health authorities, beds were provided in sufficient number to permit hospitalization of all patients with rheumatic fever, chorea, or active rheumatic heart disease, who were under 16 years of age, for a minimum period of six months, followed by adequate convalescent care and continued supervision in special centers. After this program for supervision of rheumatic children was begun, the incidence of heart disease among school children in London dropped from 2 per cent in 1926 to 0.8 per cent in 1936—a decline of 60 per cent.

That the use of a convalescent home for cardiac children is no panacea, if not preceded by an adequate period of hospitalization, has been demonstrated by experience with eighty-seven rheumatic patients who were transferred from the Children's Hospital to the Philadelphia

Heart Hospital (Table X). All children at the Heart Hospital are kept in bed for varying periods after admission, and are only gradually permitted to engage in full activity. Lavatory privileges, however, are granted from the time of admission. During the early years, many patients from the Children's Hospital were transferred to the Heart Hospital while they still had evidence of acute infection. A large proportion of these were returned with recrudescences, or with a more severe degree of functional incapacity. The death rate among such children was high. Apparently, a convalescent home is no substitute for the hospital in the case of a child with active infection, although it may serve a valuable purpose in ensuring continued supervision, adequate rest, proper diet, and schooling for the underprivileged child who has recovered from an acute attack of rheumatism. When so used, it is possible that such children may be brought into a state of good health that will insure stabilization of the infection. The subject is almost academic, however, because, save perhaps in London (prior to the present war), there have been no provisions for an adequate number of beds for long-continued hospital and convalescent care for the rheumatic child.

TABLE X

COURSE OF 87 RHEUMATIC PATIENTS TRANSFERRED TO HEART HOSPITAL

YEARS OF ONSET	NUMBER OF PATIENTS	ACTIVE INFECTION %	CLASS 11B %†	RETURNED TO HOSPITAL	WITHIN 3 YEARS	
					HRT. DIS. %	DEATHS %
1922-26	41	53.7	46.3	39.0	87.8	19.5
1927-31	27	40.7	33.3	3.7	80.1	3.7
1932-36	19	31.6*	15.8	5.2	82.4	5.2

*Active infection in children transferred during 1932-36 was usually low-grade or subclinical, in contrast to the relatively acute degree of infection which was present in many of the children who were transferred to the Heart Home during 1922-26.

†Class 11B (old terminology) indicates greatly limited physical activity due to cardiac disease.

It is the present policy of the Children's Hospital to refer to the Heart Hospital only children with minimum or moderate heart damage, who are convalescent from a first, or, at most, a second, attack of the disease, preferably with inactive infection.

Within recent years, moreover, tonsillectomy has no longer been a routine procedure in the treatment of the rheumatic child. Tonsils are now removed only when there is evidence of tonsillar disease. The operation is performed during an inactive phase of the rheumatic infection.

SUMMARY

The course of 583 children who suffered from rheumatic infection which originated during the years 1922 to 1936 has been described. Ninety-four and eight-tenths per cent of these children have been followed for a minimum period of three years and an average period of 9.6 years since the primary manifestation. At the end of this time, 64.2

per cent presented signs of valvular heart disease and 21.7 per cent had died of rheumatic infection. An additional 3.5 per cent had died of bacterial endocarditis or other infection associated with active rheumatism.

The course of the disease was modified by the type of onset; acute carditis presented the most ominous prognosis and chorea the most favorable. Children with a diagnosis of potential heart disease at the onset frequently tended to retain their freedom from signs of heart disease, in spite of recurrences.

A trend toward a decrease in the severity of rheumatic infection has been noted during the period of observation; this has been manifest especially among patients whose primary symptoms were arthritic.

This improvement in the course of the disease cannot be ascribed to racial variation, relative changes in type of onset, progressive decline in recurrences, or a modification of the policy of the hospital in regard to admissions. Although it is part of a downward trend in mortality from heart disease among young people throughout the United States registration areas, the decrease in mortality at the Children's Hospital has been greater than that in Pennsylvania as a whole.

Within recent years an attempt has been made at the Children's Hospital to concentrate attention on the child with the first manifestation of rheumatism, however mild. Such children have been kept at rest in bed and their activity restricted for longer periods of time. Whether such intensive supervision of the child with early signs of the disease has accelerated the natural trend to improvement is a subject for speculation.

A recently adopted, conservative attitude toward tonsillectomy seems at least to have had no unfavorable influence.

The experience at the Children's Hospital with patients who were transferred to a convalescent home would seem to indicate that, although such convalescent care may serve a valuable purpose in ensuring stabilization of the infection in the child who has recovered from an acute attack, it is no substitute for absolute bed rest for the child with any degree of active infection.

In spite of the seeming decline in severity, rheumatic infection still remains the most serious disease which attacks children past the age of infancy.[5, 6] In the most favorable period of the present study (1932-36), almost 7 per cent of the rheumatic children had died by the end of the first year, and 10 per cent by the end of the third year, at which time 50 per cent of the group had presented obvious signs of rheumatic heart disease.

I am indebted to the physicians and social workers from whom information was obtained; their number is too great to permit individual mention. I owe a special debt to the workers in the Social Service Department of the Children's Hospital, without whose aid many of these children could not have been traced.

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FURTHER OBSERVATIONS ON THE MECHANISM OF THE PRODUCTION OF A SHORT P-R INTERVAL IN ASSOCIATION WITH PROLONGATION OF THE QRS COMPLEX

CHARLES C. WOLFERTH, M.D., AND FRANCIS C. WOOD, M.D.
PHILADELPHIA, PA.

ALTHOUGH Wolff, Parkinson, and White[1] were not the first to report cases of short P-R intervals in association with prolonged, aberrant QRS complexes, these workers deserve the credit for directing attention to this anomaly, for making the first systematic study of it, and for pointing out that it may be found in presumably healthy persons. However, their assumption that bundle branch block is present precipitated a controversy which has continued since that time. Holzman and Scherf[2] and we,[3] independently, suggested that the anomaly might be explained by assuming that there is an accessory pathway of conduction between auricles and ventricles. We were unwilling to accept the hypothesis of bundle branch block because patients who have both normal and abnormal complexes are likely to show the same interval between the beginning of the P wave and the end of the QRS complex in both.

We shall not review the literature on the mechanism of short P-R interval and prolonged QRS complex, for this has been done many times, and again recently by Hunter, Papp, and Parkinson.[4] It is of interest that Parkinson has changed his view as to the mechanism of this condition. He no longer believes that it is a form of bundle branch block. He stresses the fact that in certain cases the P waves preceding the aberrant complexes may differ in shape from those preceding the normal complexes and states that any hypothesis should explain (1) the difference in the shape of P before normal and short P-R, bundle branch block* complexes, (2) the peculiar shape of the ventricular complex, as compared with that of ordinary branch block, and (3) the gradual change of P and QRS from short P-R, bundle branch block to normal (after atropine), and the appearance of intermediate ventricular complexes. Hunter, Papp, and Parkinson state that previous explanations did not adequately account for these facts, and they reject, among other hypotheses, that of an accessory pathway of A-V conduction. They suggest as an alternative explanation that, when the anomaly is present, the beat arises near, but not in, the normal pacemaker (for the P wave is altered)

From the Robinette Foundation, Medical Division, Hospital of the University of Pennsylvania.
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*Short P-R interval with bundle branch block complexes.

and that the normal ventricular complex is interfered with by a ventricular extrasystole which arises prematurely, low in one bundle branch. They state, "In our view the upper impulse would spread only to the ventricle other than that producing the extrasystole."

When we analyze this hypothesis, we must first admit that it could account for the aberrant complexes. Furthermore, it does away with the untenable idea of bundle branch block. The tendency of these patients to develop forms of paroxysmal arrhythmia is ascribed by these authors to hyperexcitability of the conducting tissue. They do point out, however, that the absence of ventricular extrasystoles in their cases is not in accord with the assumption of hyperexcitability.

There is one objection to the hypothesis of Hunter, Papp, and Parkinson which appears to us insurmountable. It is necessary to postulate that an ectopic ventricular beat is capable of bearing a constant time relation to an auricular beat which must be arising independently of it. Such a time relation must be maintained, not just momentarily, as might occur by chance, but over long periods of time. It appears to us that the mathematical probability of such an occurrence, not alone in one case, but in all cases of this anomaly, is not great.

Recently we have encountered a patient with this syndrome whose electrocardiogram seems to furnish further evidence on this question. In this patient's tracing (Fig. 1) the anomaly of short P-R interval and prolonged, aberrant QRS complex is exhibited. Frequent auricular extrasystoles are present, and the shape of the premature P waves differs from that of the regular P waves. The P-R intervals of the premature beats appear to be even shorter than those of the ordinary beats, but there is no essential change in the contour of the ventricular complexes. (There is a slight increase in their duration, which will be discussed below.)

This case, and a similar one reported by Scherf and Schönbrunner,[5] seem to us to add considerably to the difficulty of accounting for the syndrome on the hypothesis advanced by Hunter, Papp, and Parkinson.[4] In order to explain the aberrant ventricular complex following each auricular premature beat, one would have to assume that, whenever an auricular extrasystole occurs, a ventricular extrasystole (which must arise independently) selects the exact relative moment for its origin, which will produce a ventricular complex like all the others. Such a possibility seems to us so incredible that we believe this hypothesis, like that of bundle branch block, must be abandoned.

The question might be raised whether the behavior observed in these premature beats does not also constitute an objection to the hypothesis of an accessory pathway of conduction. In our opinion it not only does not constitute an objection, but offers further evidence in favor of it.

When a beat arises in the sinus node, the excitation process presumably travels in the manner described by Lewis to all parts of the auricles, and, in due course of time, reaches the auriculoventricular node and the accessory conduction tract, if there be such a structure. If, however, the impulse arises elsewhere in the auricles, the relative time of arrival at these two structures might remain undisturbed but is much more likely to be somewhat altered. The latter apparently occurred in our case, for the QRS complex is very slightly widened, although the P-R interval is much shorter. This suggests that the extrasystoles arose in a position relatively nearer to the accessory conduction tract than to the A-V node.

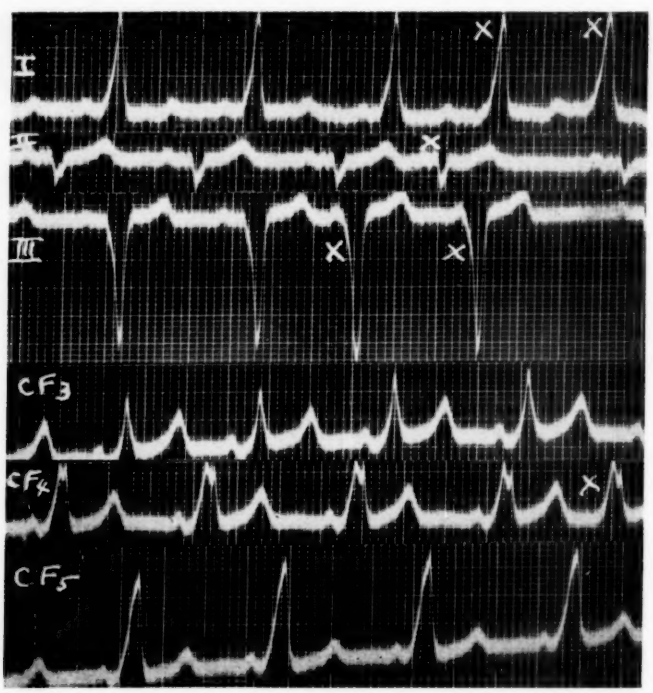


Fig. 1.—Electrocardiogram of R. M. H., a 42-year-old man who had rheumatic heart disease, with mitral insufficiency and stenosis. He had been seen on four different occasions. On Nov. 20, 1939, he had auricular fibrillation; on July 16, 1940, auricular flutter; and, on Sept. 28, 1940, normal sinus rhythm. No abnormality of the QRS complex was seen on any of these occasions. On his fourth visit Nov. 27, 1940 his tracing (reproduced here) showed the syndrome of short P-R interval and widened, slurred QRS complexes. At points marked *X*, auricular extrasystoles occurred. It will be noted that the contour of the QRS complex after each auricular extrasystole is substantially like that after the regular auricular beats, despite the fact that the P-R interval is shortened.

Holzman and Scherf[2] have suggested one other possible explanation for this syndrome of short P-R interval and aberrant QRS, i.e., that normal auricular contraction might stimulate mechanically an excitable focus in one ventricle. This seems highly unlikely for the following reasons: (1) This hypothetical phenomenon has never been observed in patients with heart block. (2) Although one (C. C. W.) of us, with McMillan, some years ago attempted to bring it about experimentally, suc-

cess was never achieved; nor do we know of its ever having been produced or observed in animals. (3) The P-R interval in Fig. 1 is shorter after the auricular extrasystoles than after the regular auricular beats. If mechanical stimulation of ventricle by auricle were taking place, the P-R interval should be essentially the same in both.

It might be worth while, in the light of recent observations, to review the present status of the hypothesis of an accessory pathway of A-V conduction. It still seems to us to be the most satisfactory explanation for this syndrome, and we have found no reason to change, in any material way, the views we expressed in our former paper.[3] In a recent paper, Glomset and Glomset[6] demonstrated the existence of accessory neuromuscular connections between auricles and ventricles. Thus the anatomic background for the hypothesis has been re-emphasized. One of the main reasons why Hunter, Papp, and Parkinson reject the "accessory pathway" hypothesis is because they found that, in certain cases, the P wave changed its contour when the aberrant ventricular complexes gave place to normal ones. Although this occurrence would not constitute a vital objection, it would be an unexpected feature if the hypothesis of an accessory conduction pathway were true. Consequently, we have consulted the papers cited by Hunter, Papp, and Parkinson in order to study the alterations in the P waves which they described. We were unable to find one of these papers, namely, that by Fernbach.[7] In the paper by Pines[8] there are no electrocardiograms. In the tracings published by Scherf and Schönbrunner,[5] the P waves do not change in the slightest way that we can see. In the tracings published by Zarday,[9] we see no change in the P waves. In the tracings published by Moia and Inchauspe,[10] there are technical defects in the curves which make analysis difficult, but one finds as much variation between the various P waves preceding the aberrant ventricular complexes as one finds when one compares them with the P waves preceding the normal complexes. In the tracings reproduced in the paper by Tung,[11] a rather interesting phenomenon is observed. Twenty minutes after the administration of atropine the P waves became smaller than they were before, and the QRS complexes returned to normal. Yet, thirty minutes after the administration of atropine, the QRS complexes were still normal, whereas the P waves had returned to their former contour. Furthermore, they retained that contour during the subsequent transition of the ventricular complexes from normal back to the aberrant configuration. This suggests that the P-wave change observed might be associated with the effect of atropine, rather than with the change of mechanism. Finally, let us study the tracings of Hunter, Papp, and Parkinson.[4] They state that P-wave changes occurred in Cases 1, 3, 5, 18, and 20. They published the tracings of Cases 1, 3, and 20. The first two show minor changes in P, not striking variations. Case 20 shows the only definite change; an inverted P in Lead I becomes upright. *But this is not an example of the*

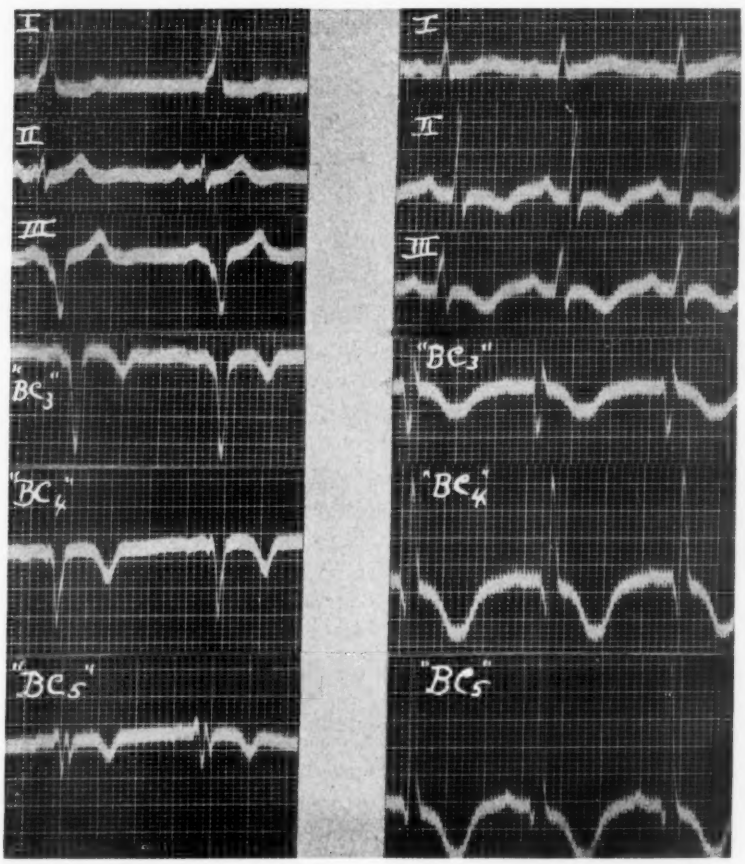
syndrome we are discussing; it shows no abnormality in the ventricular complex! Thus, after attempting a careful review of the evidence, we are impressed, not with the change which occurs in the P wave when the contour of the ventricular complex changes, but rather with the fact that the P wave shows such a remarkable constancy of contour throughout. It does not change except in minor details, which might well be explained as a result of exercise, atropine, deep breathing, or any of the other maneuvers which have been used in these cases to bring about a change in the ventricular complexes. We can say with conviction that the shape of the P waves is as constant in this group of patients, regardless of the shape of the ventricular complex, as it is in a series of tracings from patients with normal sinus rhythm.

Finally, Hunter, Papp, and Parkinson object to the hypothesis of an accessory pathway of A-V conduction on the ground that they observed ventricular complexes which were intermediate in shape between the two extremes. They state that, according to this explanation, there should be two distinct types of curves and no intermediate ones. However, according to our view, the existence of intermediate types of complexes would fit in perfectly well with the "Bundle of Kent" hypothesis. There are at least three mechanisms by which intermediate complexes might arise: (1) By a change in the conductivity of the accessory tract, (2) by a change in the conductivity of the bundle of His (in which case the time from the beginning of P to the end of QRS might change), and (3) by a shift of the pacemaker in the auricles from its usual location to a position relatively nearer to the A-V node than to the accessory tract, or vice versa. The first explanation may be the usual one. If the accessory pathway becomes less conductive under certain circumstances, one might expect the diminution of conductivity to occur gradually, with a corresponding, gradually increasing delay in the transmission of the excitatory process to the ventricular muscle. As this takes place, the area in the ventricle which is excited through the accessory pathway should become gradually smaller, and that which is excited through the bundle of His should become gradually larger. This would seem to furnish adequate reason for a gradual change in the shape of the ventricular complex as it goes from normal to abnormal.

Our conclusions are, therefore, that the hypothesis of an accessory pathway of A-V conduction is the most satisfactory one yet proposed. We have encountered no evidence to lead us to discard it. Moreover, we have not as yet heard of an alternative hypothesis which explains the phenomena observed in these cases.

There are certain other points which might be worth mentioning at this time. With regard to the question whether the part of the ventricular muscle which is activated through the accessory pathway is in the right or in the left ventricle, we[3] presented evidence suggesting that it was in the right. We now question whether this is completely justified.

Study of the electrocardiograms of right bundle branch block shows that T waves in the limb leads frequently fail to show abnormalities. This suggests that the right ventricle plays a minor part in the formation of limb lead T waves. Furthermore, in chest leads made from the C_5 position, that part of the QRS complex which is attributable to right ventricular activity is usually very small. However, in some cases of the short P-R interval and aberrant QRS syndrome, T-wave changes appear in limb leads. Moreover, in some the initial portion of the QRS complex in lead CF_5 is large. It seems likely to us, therefore, that, when



A. *B.*

Fig. 2.—Electrocardiograms of A. B., a 26-year-old man, taken on Sept. 15, 1936 and Sept. 16, 1936. (This patient was described as "Case 3" in our former paper.[3]) *A*, Tracing taken before quinidine administration on Sept. 15, 1936, showing a short P-R interval and widened, slurred QRS complexes.

He was given 40 grains of quinidine sulphate between 8 A.M. and 2 P.M. on Sept. 16, 1936. *B*, Tracing taken at 3 P.M., showing a normal P-R interval and a disappearance of the abnormality of QRS. The T-wave inversion may be a quinidine effect. Previously we had not been able o bring about a disappearance of the abnormal QRS complexes by amyl nitrite administration or by exercise. The chest leads in these tracings were taken with a polarity opposite to that now recommended by the Committee of the American Heart Association for the standardization of precordial leads. *BC3*, *BC4*, and *BC5* were taken with the right arm electrode on the precordium at C_3, C_4, and C_5 positions, respectively; the other electrode was near the angle of the left scapula.

large initial QRS deflections occur at the C_5 position, or when inversion of T_1 appears, the accessory conduction tract may be leading directly to the left ventricle, or that, at least, the excitation wave may be reaching a part of the left ventricle before that chamber is completely activated through the bundle of His.

We wish to call attention to an observation reported by Roberts and Abramson,[12] in 1936, which has not been confirmed heretofore. In a patient with this syndrome they were able to change the contour of the electrocardiogram from abnormal to normal by the administration of quinidine. We tried this same procedure on one of our patients and observed similar results (Fig. 2). The patient was described as Case 3 in our former paper.[3] On Sept. 15, 1936, he took quinidine sulphate as follows: 5 gr. at 8 A.M., 10 A.M., 12 M. and 2 P.M. (20 gr. in all) without effect. On Sept. 16, 1936, he took double the dose (10 gr. at 8 A.M., 10 A.M., 12 M., and 2 P.M.) and at 3 P.M. showed normal QRS complexes; we had been unable to bring about this change by exercise or by amyl nitrite administration. Roberts and Abramson carried out this procedure because quinidine, which is known to diminish conduction in the heart, might affect the accessory pathway more readily than it would affect the bundle of His. It should be stated, however, that quinidine also reduces the irritability of the myocardium. Consequently, this therapeutic result cannot be used as an argument in favor of the hypothesis of an accessory pathway of conduction, as opposed to that of Hunter, Papp, and Parkinson.

Finally, Scherf and Schönbrunner[5] report that, in one of their cases, large doses of digitalis caused the abnormal QRS complexes to disappear for a period of three weeks. This result might indicate that the accessory pathway is more susceptible to digitalis than the bundle of His.

SUMMARY

The syndrome of short P-R interval and prolonged QRS complex is re-examined in the light of recent observations. The hypothesis of an accessory pathway of A-V conduction is the only one thus far advanced which explains the phenomena observed in these cases.

A case is reported in which QRS maintained its abnormal contour after auricular extrasystoles. This observation renders the hypothesis of Hunter, Papp, and Parkinson even more incredible than it had seemed to us before.

Contrary to the reports of Hunter, Papp, and Parkinson, we find that the contour of the P wave is remarkably constant in these cases when the ventricular complexes change their shape.

Certain facts are presented which lead us to believe that the part of the ventricular myocardium which is activated through the hypothetical accessory pathway may not be confined strictly to the right ventricle in all cases.

The fact that quinidine will change the complexes of the electrocardiogram from abnormal to normal, as reported by Roberts and Abramson, was confirmed in one of our cases.

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ARTERIOSCLEROTIC ANEURYSMS AND SENILE ECTASIA OF THE THORACIC AORTA

MARSHALL DEG. RUFFIN, M.D., BENJAMIN CASTLEMAN, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

DEATH from internal hemorrhage, caused by rupture of the thoracic aorta in two old women with nonsyphilitic, thoracic, aortic aneurysms during the past year, has been of such unusual interest to us that we have surveyed the literature and analyzed the post-mortem records of the Massachusetts General Hospital to assemble further information about such aneurysms. The first case was one of arteriosclerotic aneurysm; the second, one of dissecting aneurysm in an aorta which was the seat of senile ectasia. We shall first present the two case histories.

CASE 1.*—(A.P.G.) A 78-year-old widow received medical attention because she was extremely nervous and mentally disturbed following an attack of vomiting. On examination she had a temperature of 101.5° F., a pulse rate of 92, a red throat, and occasional fine râles in both lungs. Her heart was within normal limits as to size, a systolic murmur was audible over the whole precordium, and there was an occasional extrasystole. The left patellar reflex was slightly greater than the right; the other tendon reflexes were normal. A blood smear showed an elevated polymorphonuclear count, but was otherwise negative. A diagnosis of mild upper respiratory infection was made. The patient was seen again a short time later by her physician because of increasing nervousness resulting from business strain; physical examination at that time showed no definite abnormalities. The blood pressure was 145/95.

A year and a half later she was examined because of fatigability, occasional shortness of breath, and slight orthopnea; she used two pillows at night. The heart borders, by percussion, were then found to be 9 cm. to the left and 3 cm. to the right of the median line. There was accentuation of the second sound, which was marked at the aortic valve area and moderate over the pulmonic valve. A short systolic murmur was heard over the whole precordium. The pulse rate was 96; the blood pressure was 140/80. The bases of the lungs were clear; the edge of the liver was not palpable; there was no edema of the ankles. After still another fifteen months she was observed after an attack of "grippe" that was accompanied by persistent pain in the region of the lower ribs on the left which

From the Department of Pathology and Bacteriology and the Medical Service of the Massachusetts General Hospital, Boston, Mass.

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*We wish to thank Dr. H. D. Stebbins, of Marblehead, Mass., for permission to use this case, which one of us (P. D. W.) saw in consultation with him. This case was discussed in detail in the Case Records of the Massachusetts General Hospital, Case 25521, New England J. Med. 25: 1030, 1939.

lasted about six days. Physical examination revealed an increase in the anteroposterior diameter of the chest, with hyperresonance except at the left base below the midscapular region, where there was slight dullness, with vesicular breath sounds throughout, without râles, but with a slight decrease in the intensity of the breath sounds below the left scapula. The border of cardiac dullness was 8 cm. to the left of the midline in the fifth intercostal space and 3.5 cm. to the right in the fourth. The sounds were distant but clear. There were no murmurs. The blood pressure was 130/80 in both arms, and 150/90 in both legs. There was no tracheal tug. The pupils were equal and reacted to light and in accommodation. The peripheral vessels showed a rather marked degree of arteriosclerosis. A roentgenogram of the chest (Fig. 1), made with a portable machine, showed a large round mass, apparently continuous with the heart shadow, occupying the entire middle third of the left lung field. An electrocardiogram showed a sinus tachycardia of 135 beats per minute, with left axis deviation (−22°), a P-R interval of 0.13 sec., and notched P_3 and P_4; QRS_1 and QRS_2 were of fairly low voltage (6 mm. and 5 mm., respectively); the S-T segments in Leads I and II sagged slightly; T_1 and T_2 were upright; T_3 was shallow and inverted; R_4 was present; and T_4 was upright. A blood Wassermann reaction was negative.

Fig. 1.—Roentgenogram of thorax of A. P. G., Case 1 (aged 82), showing large aneurysm of the descending thoracic aorta.

Three months later, at the age of 82 years (four years after her first complaints), she spent a busy day shopping, apparently feeling quite well. She went to bed at 9:00 P.M. after a good New England supper of baked beans and brown bread, and slept quietly until midnight, when she suddenly awoke complaining of severe pain in the mid-upper back and chest. She became extremely orthopneic and dyspneic. On the arrival of her physician, a few minutes later, she was found sitting up in bed breathing forty to fifty times per minute. Her pulse rate was 140, and the pulse was weak. She was wild-eyed and had an ashen cyanosis, with cold sweat. The peripheral veins were not distended. The heart sounds were distant but clear. There were no murmurs. The lungs were clear throughout; there were no râles even at the extreme bases. The abdomen was negative. The patient

was given ¼ grain of morphine sulfate and 1/150 grain of atropine sulfate subcutaneously. Although the rapid respiration persisted, she soon became unconscious. At about 1 A.M. the radial pulse became imperceptible and the blood pressure could not be measured. Oxygen was given for an hour. An electrocardiogram showed a ventricular and auricular rate of about 130, with slight left axis deviation, upright T_1 and T_2, and an inverted T_3; the P-R interval was 0.15 sec., with slightly elevated S-T segments in Leads I, II, and III, and low QRS voltage. The patient was given coramine and caffein sodium benzoate, but expired about two and a half hours after the onset of the attack. The clinical diagnosis was ruptured aneurysm of the thoracic aorta.

The autopsy revealed the body of a well-developed and nourished, moderately obese, 82-year-old, white woman who had multiple arteriosclerotic saccular aneurysms of the aorta, with rupture of one in the descending thoracic portion into the right pleural cavity. There resulted a massive hemothorax containing approximately 2 liters of fresh, deep-red blood, some of which had clotted post mortem. When this blood was removed and the right lung pulled forward, the mediastinal parietal pleura along the anterior portion of the thoracic vertebrae was seen to be colored purplish red by blood which was beneath it. In this region, at the level of the fourth dorsal vertebra, there was a triangular tear, measuring 1 by 0.5 cm., which was apparently the source of the pleural hemorrhage. The left pleural cavity contained approximately 200 c.c. of clear, straw-colored fluid. The lower two-thirds of this cavity were replaced by a large lobular mass, measuring 12 by 12 by 8 cm., which compressed the lower lobe of the left lung and produced definite atelectasis. The remainder of the lungs and the heart were not remarkable. The ascending portion of the thoracic aorta was fairly smooth and showed no aneurysm. The arch revealed moderate arteriosclerosis, with some ulceration. Most of the descending thoracic portion of the aorta was composed of a huge aneurysmal sac which extended out from the left lateral wall. This aneurysm measured 12 cm. in length by 12 cm. in width, and had a round opening into the aorta of a diameter of 8 cm. It was completely filled with grayish-red, solid thrombus. On the right anterior lateral wall of the aorta, at a point approximately level with that of the aneurysm, the intima was completely denuded and eroded over an area measuring 5 by 3 cm. This area was covered by a yellow-gray, friable mural thrombus. There was another similar area, about 1 by 5 cm. in extent, just medial to the larger erosion. Blood clot from the aneurysm extended beneath the former erosion around the posterior aspects of the aorta into the right side, through which it ruptured into the right side of the thorax via the mediastinal parietal pleural tear previously noted. Over the lower lumbar vertebrae there was a large firm mass, 12 cm. in length by 5 cm. in width, which, when removed, was found to be another atherosclerotic aneurysm with an aortic opening about 6 cm. in diameter. It involved the whole anterior portion of the aorta and was filled with firm, red-gray thrombus. There was still another aneurysm, 5 by 5 cm. in diameter, involving the left common iliac artery. The aorta between the aneurysms showed marked arteriosclerosis throughout, with ulceration and small mural thrombi. The other gross anatomic abnormalities were of little import. Microscopically, sections through the aneurysms showed marked fibrous intimal proliferation, slight lymphocytic infiltration of the media, and an old organized thrombus attached to the intima. There was no evidence of syphilis.

CASE 2.—(M. Van d.P.) A 71-year-old housewife entered the hospital in January, 1934, because of shortness of breath of a month's duration. For ten years the patient had experienced slight shortness of breath and occasional staggering while walking. Her physician had found hypertension and had treated her with "powders" and tablets. During the month preceding admission, however, she

noted increased dyspnea and palpitation and a feeling of constriction in the precordial region on slight exertion. She also noticed pyuria, burning urination, and a foul odor to the urine.

The examination showed generalized arteriosclerosis, but no congestive failure. The heart was moderately enlarged, and there was a questionable systolic thrill to the right of the upper end of the sternum. The apical impulse was vigorous. Maximal to the right of the upper and middle portions of the sternum was a loud, harsh, systolic murmur. The aortic second sound was present, and was followed by a slight to moderate diastolic murmur. The heart rate was 70 per minute, with frequent premature beats. The blood pressure was 165/96, and alternation was present. An electrocardiogram showed auricular premature beats, a rate of 60 to 65, a diphasic T_1, and moderate left axis deviation.

She remained in the hospital for two weeks, and was discharged improved, on digitalis, with a diagnosis of hypertensive and calcareous valvular heart disease, with aortic stenosis and regurgitation.

Second admission, September, 1936. This illness was apparently due to cholecystitis and pneumonia, which precipitated an ectopic auricular tachycardia at a rate of 340, with 2 to 1 block and mild failure. She was seriously ill for two weeks. The block was increased to 4 to 1 with digitalis. Later, auricular fibrillation appeared, and, still later, normal rhythm returned spontaneously. The patient was greatly improved. The lung signs disappeared, and, although mild attacks of abdominal discomfort continued, it was felt that surgical treatment was not indicated.

In November, 1936, the patient returned for examination feeling quite well except for a little indigestion (occasional gaseous distention and mid-abdominal pain). She looked well. Her pulse was regular at a rate of 72. Her blood pressure was 160/80. The heart was large, and there were moderately loud aortic systolic and diastolic murmurs, with slight thrills palpable in both systole and diastole. The aortic second sound was accentuated. The electrocardiogram showed normal rhythm, a rate of 65, moderate left axis deviation, and sagging S-T segments in Lead I (a digitalis effect). Fluoroscopic examination revealed a big, round, active heart, with a very dense, dilated, actively pulsating ascending aorta. The lung hila were normal in appearance. By orthodiagram, the transverse diameter of the heart measured 14.6 cm. and the internal diameter of the thorax 21.5 cm.; the width of the great vessels in the anteroposterior view was 8.3 cm.

On June 29, 1937, at the age of 75, she had a paroxysm of auricular fibrillation during a routine examination, and her heart and aorta were somewhat larger than the year before; a note was made that, fluoroscopically, the ascending aortic shadow resembled that of an aneurysm.

In January, 1938, she complained only of occasional palpitation, not of pain or dyspnea. Her heart was larger, measuring 16.1 cm. in its transverse diameter by orthodiagraphy. The electrocardiogram now showed inversion of the T waves in Leads I and IV, in addition to considerable left axis deviation.

In June, 1938, she at last showed frank heart failure, which had begun with orthopnea at night a week before. She had been seriously ill with grippe and pneumonia in April. Examination revealed moderate edema of both feet, an increased jugular pulsation, a blood pressure of 145/90, a larger heart (16.6 cm. transverse diameter by orthodiagraphy), and a pulse rate of 84, with occasional extrasystoles.

With rest and digitalis the failure subsided, and, in December, 1938, she was well except for dyspnea on effort. Examination revealed no congestion except of the hila of the lungs, as shown by fluoroscopic examination. The murmurs over the aortic valve area were now clearly continuous, with a systolic accentuation and thrill. Aneurysmal dilatation of the ascending aorta was evident fluoroscopically,

and, because of the change in the character of the murmur and the development of heart failure, a question was raised as to dissection or rupture.

The last routine examination took place in June, 1939. She had been fairly well through the winter except for dyspnea and weakness. There had been no cough or chest pain. The continuous murmur and thrill over the aortic valve area were more evident than before. Fluoroscopic examination showed kinking and bulging of the descending aorta as well as aneurysmal dilatation of the ascending aorta, and a diagnosis of probable arteriosclerotic aneurysmal disease of the aorta with questionable rupture into the right side of the heart or pulmonary artery was made. A roentgenogram (Fig. 2) showed marked enlargement of the heart on both sides, but chiefly in the region of the left ventricle. The aorta was markedly tortuous, dilated, and calcified. A lateral view (Fig. 3) showed the marked dilatation of the ascending aorta and the extreme calcification of the arch and descending portions. She went to California that summer and, after returning, was confined to her home because of dyspnea. In November, 1939, she quietly passed away without any noticeable signs to suggest rupture of an aneurysm.

Fig. 2.—Roentgenogram of thorax of M. Van d.P., Case 2 (aged 76), showing senile ectasia of the ascending aorta, marked calcification of the aortic arch, and a very large heart.

The post-mortem examination revealed a well-developed and moderately well-nourished, previously embalmed, 76-year-old woman who weighed approximately 100 pounds. The lungs showed apical scars and slight but definite emphysematous changes. There were no areas of consolidation. A few large blood clots, measuring altogether roughly 7 by 3 by 2 cm., were found high in the pericardial cavity, especially surrounding the aorta and pulmonary artery. The heart weighed 500 grams. The right ventricular wall measured 7 mm. in thickness, the left, 20 mm. There was marked hypertrophy of the left side of the heart; the right ventricle formed only a small portion of the anterior surface. *All of the valves were normal.* The coronary arteries showed moderate arteriosclerotic changes, with calcification in many places, but no evidence of occlusion. The whole ascending aorta was

markedly dilated, forming a diffuse aneurysm which measured approximately 12 cm. in circumference. The intima was smooth throughout, with very little atheroma and no scarring. There were numerous trocar incisions (embalmer's) throughout the whole wall of the aorta in this portion, which made it difficult to ascertain whether any of these tears in the intima occurred ante mortem. There was a dissecting aneurysm, filled with fresh blood, which extended from the base of the valve to the beginning of the arch, and involved the anterior and lateral portions of the aortic media. Extravasated blood was present around the adventitia of the intrapericardial portion of the aorta, and especially of the pulmonary artery, where a large amount of blood was extravasated into the adventitia, forming a large hematoma approximately 3 by 2 by 1 cm. The dissection stopped abruptly at the beginning of the arch. Both the arch and descending portion of the aorta

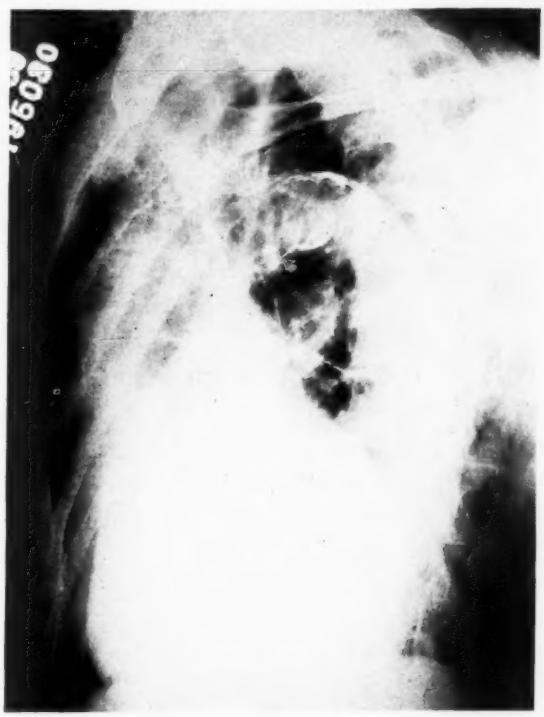

Fig. 3.—Roentgenogram of the left, anterior, oblique view of thorax of M. Van d.P., showing calcified, tortuous aortic arch and descending aorta, and aneurysm and dilatation of the ascending aorta.

showed extreme arteriosclerotic changes, with extensive calcification, forming a rigid, calcareous tube which was very brittle. The circumference of the arch was 8 cm., and that of the descending portion, 7 cm. The intima showed marked arteriosclerosis with numerous ulcerated areas. No mural thrombi were seen. The dissection ended so abruptly when it reached the arch, where the arteriosclerosis was extreme, that it seemed quite possible that the mechanical rigidity halted its course. The splenic and renal arteries were markedly tortuous, calcified, and extremely rigid. Microscopic sections of the ascending portion of the aorta revealed slight to moderate atherosclerosis. The dissection was present in the outer portion of the media, and was composed of recent blood clot. Other sections showed small foci of medial degeneration, with occasional changes suggestive of cyst formation.

Stimulated by these two striking cases, we deemed it of interest to review the autopsy cases of aortic aneurysm at the Massachusetts General Hospital.

Among 9,600 post-mortem examinations which had been done since 1897 at the Massachusetts General Hospital, there were 116 cases of aneurysms of all sorts involving the thoracic and abdominal aorta, or 1.2 per cent of the total number of necropsies. Of this group seventeen were cases of true dissecting aneurysm with medionecrosis aortae cystica, and thirteen were cases in which small "dissections" had occurred mostly in and about small atherosclerotic plaques. None of these thirty cases are within the scope of this paper. Of the remaining saccular, fusiform, and cirsoid aneurysms, there were eighty-six cases in which the aorta was involved, roughly as follows: twenty-one in the ascending aorta, thirty-seven mainly in the arch, and eight in the descending thoracic portions; there were twenty aneurysms in the abdominal aorta.

Of the sixty-six thoracic aneurysms, sixty were syphilitic and three were definitely arteriosclerotic; in three cases there was marked dilatation of the ascending aorta without arteriosclerosis—a condition we are calling "senile ectasia."

In one of the arteriosclerotic cases (Case 1) and one of the senile ectasia group (Case 2) rupture occurred, as described above in detail.

The two other arteriosclerotic cases may be briefly summarized. One was that of a 70-year-old woman who died of rupture of a dissecting aneurysm of the ascending aorta. At a point about 10 cm. below the aortic arch, just above the diaphragm, there was an ovoid aneurysmal sac about 7 by 5.5 cm., partly filled with old thrombus. There was no communication between this sac and the dissecting aneurysm above; it was regarded as a separate arteriosclerotic aneurysm.

The third case of arteriosclerotic, thoracic, aortic aneurysm was that of a 90-year-old man who died of bronchopneumonia following reduction of a strangulated hernia. Here there was a fusiform, severely arteriosclerotic dilatation of the ascending aorta measuring 9.5 cm. in circumference. Further evidence of its arteriosclerotic nature was the presence of a similar but larger aneurysm of the abdominal aorta.

The second of the two remaining cases of senile ectasia was that of a 67-year-old man who died of acute coronary thrombosis. The ascending aorta was smooth, showed very little atheromatous change, and measured 10 cm. in circumference. Its elasticity was markedly diminished.

The third case* of senile ectasia was one in which the aneurysmal dilatation was so large that it had produced dilatation of the aortic ring and aortic insufficiency, and was considered clinically as syphilitic aortitis with involvement of the aortic valve. The patient was a 70-year-old man who had had dyspnea and palpitation on exertion for many years. He first consulted his physician one week before admission because of dyspnea and edema of the legs. When examined in the emergency ward he was semicomatose. There was marked pulsation of the neck vessels, and a pulsating mass was felt behind the suprasternal notch. The heart was greatly enlarged, and the supracardiac dullness measured 10 cm. There were loud systolic and diastolic murmurs at the base of the heart. The blood pressure

*This case was discussed in detail in the Case Records of the Massachusetts General Hospital, Case 18162, New England J. Med. **18**: 861, 1932.

was 200/55. The pulse was Corrigan in type, and Duroziez's sign was present. The Hinton test was negative. Post-mortem examination showed a tremendously dilated, inelastic ascending aorta which measured 15 cm. in circumference (Fig. 4). The intima was perfectly smooth, and neither grossly nor microscopically was there any evidence of either syphilis or atherosclerosis.

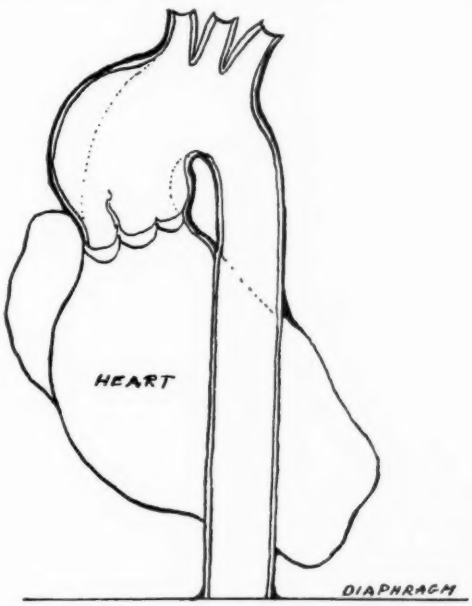

Fig. 4.—Diagram of heart and aorta of a third patient of the present series of senile ectasia (man of 70 years). The dotted lines represent what should be the normal contour of the ascending aorta and the aortic arch.

Of the twenty abdominal aortic aneurysms, only three were syphilitic; the other seventeen were arteriosclerotic. All of the former and six (or one-third) of the latter ruptured. The average age at death in the entire syphilitic group of sixty-three cases was 46.4 years, and in the arteriosclerotic and senile ectasia group of twenty-three cases, 72.7 years (the three patients with senile ectasia averaged 71 years).

DISCUSSION

Since the time of Galen medical interest in arterial aneurysms has been as widespread as the knowledge of the etiologic and pathologic aspects has been vague. Before the discovery of the *Spirochaeta pallida*, most aneurysms, especially the nontraumatic, noncongenital varieties, were thought to be caused by arteriosclerosis. But afterwards, as the disease syphilis became better understood and its pathology widely known, the etiologic pendulum swung to the other extreme. In 1928, MacCallum[1] stated that "true aneurysms are the result of syphilitic disease of the wall of the vessel." Two years later, however, Korns[2] presented two cases of undoubted atherosclerotic aneurysm of the thoracic aorta which occurred, in each instance, in elderly persons who had

marked atherosclerosis elsewhere in the larger arteries and no serologic or pathologic evidence of syphilis. These cases gave undoubted proof of the etiologic role which atheroma may play in the production of aneurysm. Karsner,[3] however, averred in 1938 that only rarely are aortic aneurysms the result of intimal arteriosclerosis except in the abdominal aorta, where it is a cause in a fair number of cases. The relative importance of such aneurysms in the future becomes apparent when one considers, on the one hand, a constantly aging population with its now inevitable increase in atheroma and the consequent increase in the frequency of arteriosclerotic aneurysm, and, on the other hand, a steadily declining incidence of syphilis in the masses.

In discussing the clinical aspects of thoracic aneurysms, Mills and Horton[4] stated that approximately 85 per cent of thoracic aneurysms are said to be syphilitic, and most of the remaining ones arteriosclerotic. In their series, 70 per cent of the patients (total of 339) had syphilis, and in the remaining 30 per cent there was no history of syphilis or evidence of the disease. In 18 per cent of the latter group, arteriosclerosis of the higher grades ("3 to 4 plus") was present, but they were careful to admit that without suitable anatomic confirmation this association did not permit one to assume that atherosclerosis was the cause of the aneurysm. Because of the advanced age of the patients in the series, it was concluded that arteriosclerosis was probably an etiologic factor in a large number. No anatomic studies were done.

Only a few years ago the clinician considered it an axiom that all large aortic aneurysms were syphilitic in origin; small mycotic or infectious aneurysms were admitted as possibilities to be diagnosed rarely, if ever, during life. Hence, whenever it was obvious clinically or roentgenologically that an aneurysmal dilatation of the aorta was present anywhere, whether in the ascending or descending portions or in the arch, little or no doubt was entertained that the patient had old syphilitic infection, no matter what the history, serologic reaction, sex, or age of the patient might be, or even what the pathologist might have to say.

Meanwhile the pathologist had become convinced, with the passage of time, that, occasionally, large aneurysms of the aorta are not syphilitic in origin, but are arteriosclerotic in nature or of the type of so-called senile ectasia in which a loss of elasticity allows a chronic ballooning out of the ascending aorta, without atheroma or calcification. It is common knowledge, of course, that arteriosclerosis of the aorta is itself precipitated or speeded up by an underlying syphilitic aortitis which may be more or less concealed by the sclerotic process that overlies it, but in the cases with which we are now concerned, no such basis could be discovered by careful search.

Slight to moderate dilatation of the ascending aorta with advancing age is not an uncommon post-mortem finding, and it is usually ex-

plained as the result of a decrease in elasticity. Numerous studies on this subject,[5-7] testing the elasticity of both whole aortas and strips of aorta, have all shown that there is a definite diminution of elasticity with the process of senescence. Microscopic examination of sections stained for elastic tissue does not, however, reveal any such change. Elastic fibrils still remain, but it is quite possible that, although they continually take the elastic tissue stain, they have lost their functional elasticity. Recently, Krafka[8] has shown that 20 per cent of the loss in elasticity of the aorta with age results from fibrosis. The extreme degree of ectasia that was seen in the cases cited, however, is certainly unusual.

Just as in the case of dissecting aneurysms, so too in that of arteriosclerotic aneurysmal sacs, the pathologist was well in advance of the clinician in his knowledge of aortic disease. But he kept this knowledge too much to himself, or we might better say that the clinician did not ask to be instructed. Incidentally, the details of coronary artery disease are perhaps the most glaring example of the slowness with which the pathologist's knowledge penetrated the sickroom. Finally, five or ten years ago, internists began very slowly to learn that abdominal aortic aneurysms might be entirely arteriosclerotic in origin, and, moreover, might rupture and cause rapid death. We are sure that many physicians who are not yet past middle age had no such teaching in their early days in medicine.

And now we realize, from such cases as we have recounted above, that even large *thoracic* aortic aneurysms may be of an arteriosclerotic or senile nature, and that they too may rupture, with fatal hemorrhage.

An important clue to the diagnosis of arteriosclerotic aneurysms and senile ectasia of the thoracic aorta, in some cases at least, is the combination of old age, female sex, and negative serologic reaction. Recognition of this condition and proper diagnosis are of more than academic interest, for neither should such aneurysms stigmatize the patient as syphilitic, nor should the patients receive antisyphilitic therapy, which is a tedious, costly, unnecessary, and, indeed, hazardous procedure in these old people.

There remains to be explained the continuous murmur which was heard over the markedly dilated ascending aorta in the case of the old lady with senile ectasia (Case 2). The systolic and diastolic murmurs which were heard at first in her case are easily explained on the basis of the dilated aorta and stretched aortic valve ring, but the superimposed continuous murmur is not so easily accounted for in the absence of an arteriovenous or interarterial communication, the diagnosis of which was hazarded because of this murmur. Very likely continuous eddies in a large, nonthrombosed sac like this can produce such a murmur, in accordance with the old-fashioned idea.

SUMMARY AND CONCLUSIONS

1. Two case records of elderly women are presented, in which death resulted from rupture of nonsyphilitic aneurysms of the thoracic aorta; one was arteriosclerotic and the other was associated with senile ectasia.

2. Two other cases of arteriosclerotic aneurysm and two more of senile ectasia of the thoracic aorta were discovered on review of the remaining 9,600 autopsy records of the Massachusetts General Hospital. Among these same autopsies there were sixty syphilitic aneurysms of the thoracic aorta, only three syphilitic aneurysms of the abdominal aorta, and twenty-seven arteriosclerotic aneurysms of the abdominal aorta.

3. Middle age (46.4 years) was the average length of life for the syphilitic group, while old age (72.7 years) was the rule when the aneurysms were caused by arteriosclerosis or senile ectasia.

4. As a result of a constantly aging population and a gradual reduction of the incidence of syphilis in the masses, it is postulated that the importance of arteriosclerotic aneurysms and senile ectasia will increase in the coming years, and that these conditions will be more commonly found if more autopsies are performed on aged persons who have hitherto failed to attract interest beyond a customary diagnosis of arteriosclerosis or senility on their death certificates.

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THE NORMAL AND ABNORMAL ESOPHAGEAL ELECTROCARDIOGRAM, WITH PARTICULAR REFERENCE TO MYOCARDIAL INFARCTION

JAN NYBOER, D.Sc., M.D.
NEW YORK, N. Y.

THE concept of the electrical field of the heart in acute coronary disease has been greatly broadened by the use of exploratory precordial leads. The well-known contributions of Wilson, et al.,[1-3] and of Wolferth, et al.,[4-6] which led to the routine use of the precordial lead, have established the validity of the exploratory method in making a positive diagnosis of anterior myocardial infarction.

Following the work of Lieberson and Liberson[7] and of Brown,[8] Hamilton and Nyboer[9] proposed using an esophageal electrode for localizing and evaluating posterior ventricular infarcts. In the present investigation, cases have been observed in which the onset of coronary occlusion ranged from one day to sixteen years prior to study by the esophageal leads. In these same cases, standard electrocardiograms and exploratory electrocardiograms of each extremity and of several positions on the precordium were also recorded.

Hamilton and Nyboer[9] and Nyboer[10] showed that the auricular intrinsic waves of Lewis were present in the P waves which were recorded from the auricular level and absent in those recorded below and above the auricular level. It was possible, therefore, when the pacemaker was in the region of the sinus node, to differentiate electrocardiograms from the left auricular and left ventricular levels by taking serial esophageal leads at 2.5 cm. steps between the lowest and highest levels. P waves were selected from esophageal electrocardiograms which usually resembled those in standard Leads I and II, without intrinsic deflections, and the ventricular levels were ascertained from multiple esophageal leads on normal and abnormal subjects. An attempt was made to show that the esophageal electrocardiogram from the ventricles is as specifically diagnostic of posterior myocardial infarction as the precordial electrocardiogram is diagnostic of anterior wall infarction.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, New York City.

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It will also be shown that the criteria for a diagnosis of posterior myocardial infarction by the esophageal ventricular lead are essentially the same as those employed for a diagnosis of anterior myocardial infarction in the precordial lead.

NOMENCLATURE AND METHOD

The standard leads were marked I, II, and III. A selected precordial lead, marked IV, was taken from the region of the apex, or V_4 to V_6 region of Wilson. The selected juxtaventricular lead in the esophagus was marked EV, and hereafter will be referred to as "EV lead." The selected juxta-auricular lead in the esophagus was marked EA, and will be referred to as "EA lead." The esophageal tracings were usually perforated with the distance in centimeters from the nares or incisor teeth to the retrocardiac exploratory level. The limited or selected leads were used in order to illustrate the more significant observations with relation to the anterior and posterior wall of the heart, although complete data were available in each case.

The central terminal of Wilson, Johnston, Macleod, and Barker was used as the indifferent electrode in the precordial, extremity, and esophageal leads. All exploratory leads were recorded in such a way that an electronegative deflection was a downward movement on the graph, and thus they conform to the new terminology for exploratory electrocardiograms recommended by the American and British Heart Associations. The usual level for study of the posterior part of the heart ranged between 30 and 60 cm. from the incisor teeth or nares. The patient was usually in the recumbent position while the esophageal ventricular leads were being recorded. This was helpful in probably preventing excessive overlapping of the left auricle over the left ventricle, which would have confused the electrical picture in this region.

Since the roentgenkymographic studies of Gubner and Crawford[11] on coronary thrombosis appeared simple and diagnostic, it seemed that their method might possibly be used as a check on the validity of the esophageal electrocardiogram. Hence, a No. 14 soft rubber tube was equipped with a whalebone insert upon which radiopaque metal rings were mounted and properly spaced. This esophageal tube was used to identify the posterior levels of the heart in the conventional or kymographic roentgenograms. The observations in two cases of typical posterior myocardial infarction will be presented by this method; the records were made with the patient in the standing position.

RESULTS

A. The Normal Esophageal Lead

In each of four normal subjects (D. B., aged 22, E. G., aged 26, and D. K., aged 40, in Fig. 1, and R. W., aged 26, in Fig. 2) a close resemblance was noted between the potentials of the selected Lead IV and the EV lead, in spite of minor deviations in electrical axis as shown in the standard leads. At the esophageal auricular level the QRS complex and the T wave were usually approximately inverted images of the normal ventricular potentials in the apical and esophageal ventricular leads. P in Lead EA showed intrinsic waves which were easily identified at several levels.

In each EV lead the P waves showed no evidence of intrinsic deflections, and were usually smooth, convex, and upright. The ventricular complex was usually composed chiefly of an R wave. A small Q wave was rarely present, and was not considered abnormal clinically unless it exceeded 0.4 millivolt, and was present with other abnormalities. The S wave could normally be absent. The RS-T segment was approximately isoelectric. The T wave was usually convex, upright, and definitely electropositive in all normals. Deviations from these findings were considered abnormal in the following cases.

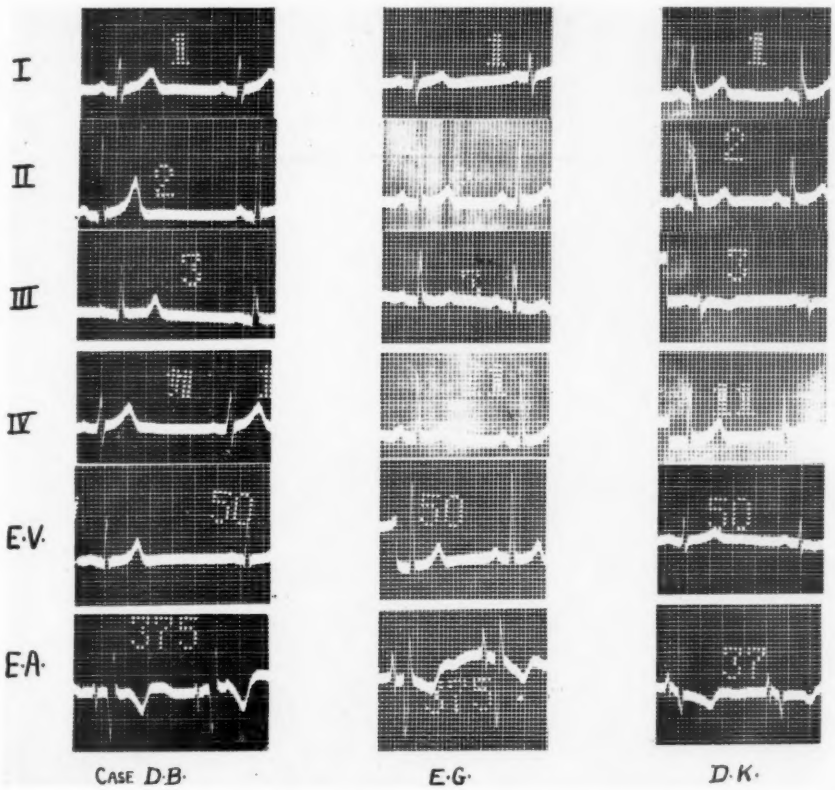

Fig. 1.—Standard, precordial, and esophageal electrocardiograms on three normal subjects, showing the close similarity between Lead IV and Lead EV. Note that the QRST deflections in EA are essentially inverted images of QRST in EV and $QRST_1$.

B. Anterior Myocardial Infarction

B. C. (a man, aged 49), previously cited by Hamilton and Nyboer,[9] showed abnormalities in the standard and fourth leads, which, together with a typical clinical history and course, appeared sufficient for a diagnosis of anterior myocardial infarction. Six weeks after the onset of the disease, the precordial lead (Fig. 2) showed an abnormal Q as the sole QRS complex, and a sharply inverted T wave. These abnor-

malities, together with the progressive change observed previously, were diagnostic of anterior myocardial infarction.

The EV potentials in this case resembled the esophageal ventricular potentials of normal subjects; however, minor abnormalities of the RS-T segments and T waves were present. The EA potentials were markedly abnormal in this case; the initial and final ventricular complexes were essentially inverted images of potentials from the precordium over the "central area" of infarction (Fig. 2).

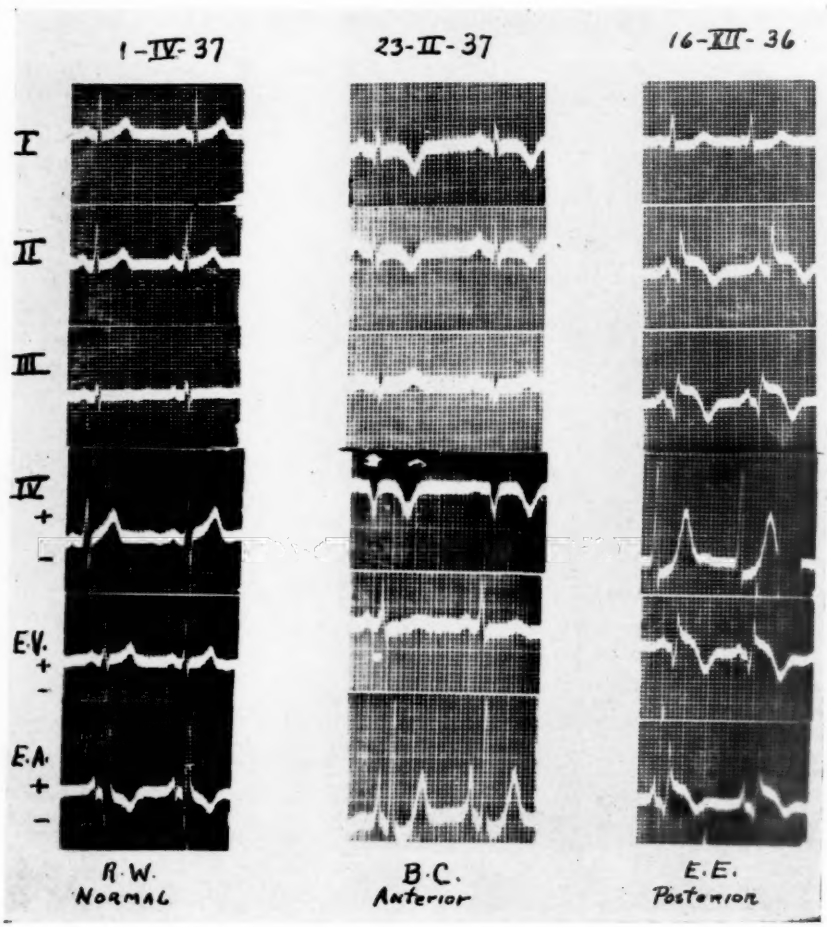

Fig. 2.—Comparison of tracings from a normal subject with those in cases of anterior and posterior coronary occlusion, using standard and selected exploratory leads. (These tracings were modified and reprinted by permission of the authors, Hamilton and Nyboer[9].)

C. Recent and Healing Posterior Myocardial Infarction

CASE 1.—E. E., a man, aged 59, previously cited by Hamilton and Nyboer,[9] suffered a typical attack of coronary occlusion. The usual four leads supported the clinical diagnosis and indicated that the occlusion was a posterior one (Q_3T_3 type).

One day after the onset of the disease, the EV potentials resembled Lead III (Fig. 2) and the left leg extremity potential (not shown). The authors commented that these curves were comparable to those which are obtained at the margin of experimental infarcts, as shown by Wilson and his collaborators,[3] and that the infarct probably did not involve the entire thickness of the muscle under the electrode. In esophageal Lead EV the Q wave was about one-third the size of the QRS, and was associated with a markedly elevated RS-T segment and inverted T wave. The juxta-auricular leads were also abnormal and showed a small Q wave, a tall R wave, an elevated RS-T segment, and a diphasic T wave.

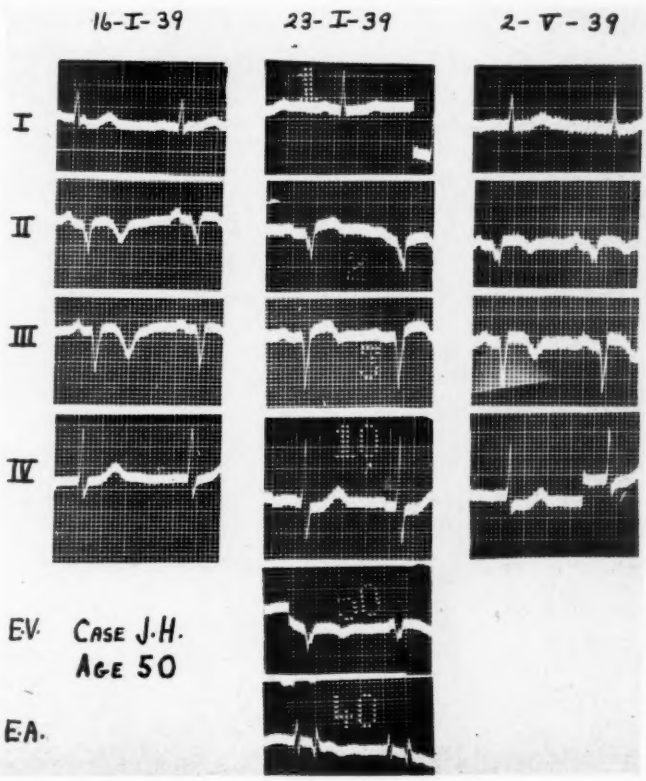

Fig. 3.—Three electrocardiograms on a patient with posterior coronary occlusion, showing an abnormal Q in EV as the sole QRS deflection, accompanied by inversion of T in EV.

CASE 2.—J. H., a man, aged 50, had a typical attack of coronary occlusion while at work (January 14). A few hours later this diagnosis was confirmed by a four-lead electrocardiogram in his physician's office, and the patient was hospitalized. On the third hospital day, January 16, a tracing of the Q_3T_3 (Fig. 3) type indicated that the occlusion was posterior, but Lead IV was not definitely abnormal.

On the ninth hospital day, January 23, esophageal lead EV (Fig. 3) showed a Q wave as the sole QRS deflection, an inverted T wave, and an isoelectric RS-T segment. The corrected Q wave measured 1.5 millivolts, and the T wave was negative by 0.3 millivolt. The EA lead was not definitely abnormal. Thus the progressive and marked RS-T and T-wave changes in the standard leads, with the persistently abnormal Q_2 and Q_3, established the correctness of the diagnosis of posterior myocardial infarction; this was also supported by the EV lead changes.

A four-lead electrocardiogram on May 2 (Fig. 3), taken two days after the second attack of coronary occlusion and 3.5 months after the first occlusion, suggested the possibility of a superimposed, recent, posterior myocardial infarction. The patient died on May 3. Necropsy was not permitted.

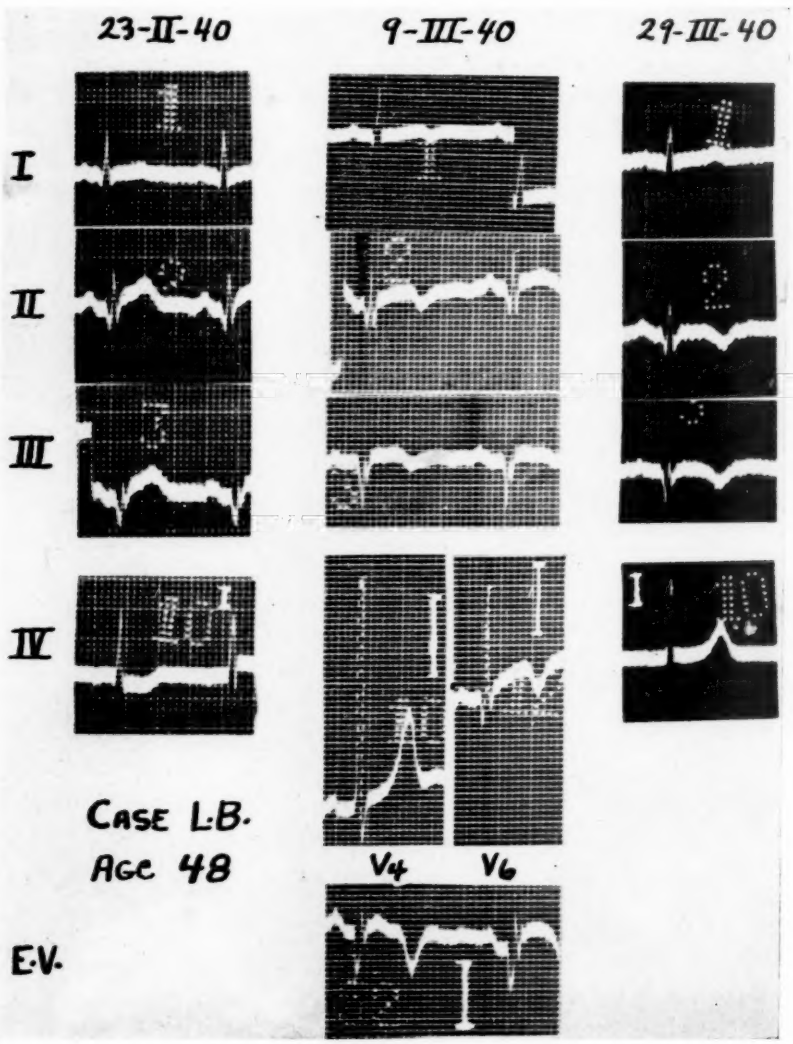

Fig. 4.—Three electrocardiograms on a patient with coronary occlusion, showing abnormalities in the EV lead which indicate that the myocardial infarct is posterior. (Variations in the standardization of the EV lead and Lead IV are indicated by the vertical white lines.)

CASE 3.—L. B., a man, aged 48, was well until two months before admission to this hospital, when he first complained of intermittent "indigestion." About one week before entry he had suffered from acute, localized, precordial distress without radiation; it lasted a few hours and was relieved by a "hypodermic injection." An electrocardiogram taken a few days later was said to have been abnormal; the industrial physician, however, permitted him to return to work the same week.

One day before entry he had a second, severe attack of precordial distress which was not relieved by 5 nitroglycerine tablets. It persisted for about four hours.

A four-lead electrocardiogram on admission (Fig. 4, February 23) showed an abnormal Q_2 and Q_3, an elevated RS-T_2 and RS-T_3, a depressed RS-T_4, and an upright T_2 and T_3. These abnormalities, together with progressive changes in the next twenty-four hours and the history, were adequate to establish a diagnosis of very recent myocardial infarction involving mainly the posterior ventricular wall. The precordial series (Fig. 4, March 9) showed an essentially normal V_4, but an abnormal V_6, which was probably indicative of an associated, incomplete infarction of the apex. Additional, progressive, standard lead changes were apparent on March 29 (Fig. 4).

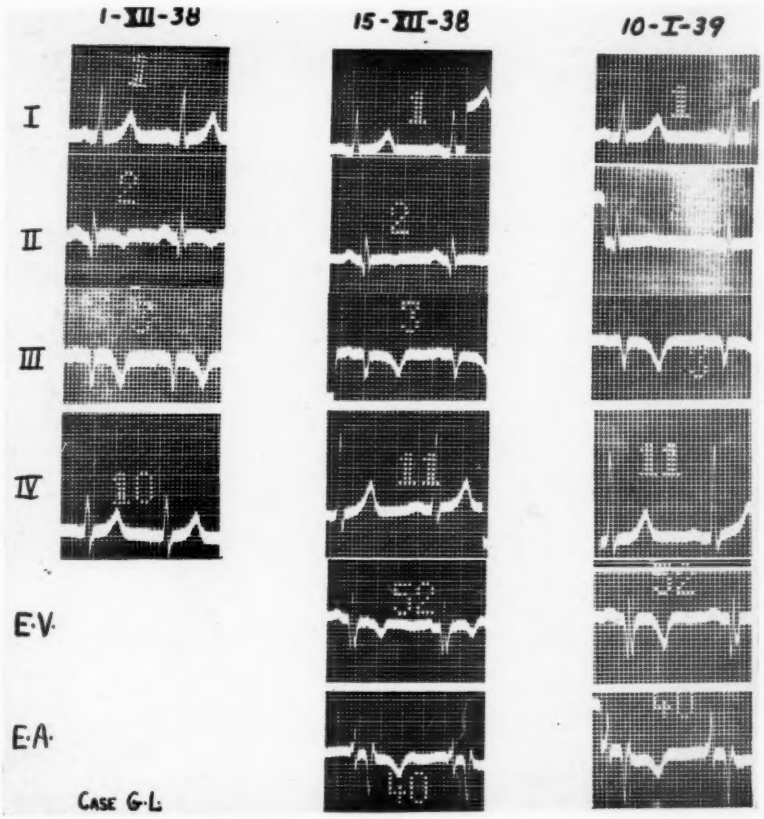

Fig. 5.—Three electrocardiograms on a patient with posterior myocardial infarction, showing persistence of the EV abnormalities after a three-week interval.

Esophageal Lead EV (Fig. 4, March 9), about three weeks after the onset of acute symptoms, showed an abnormal Q of 0.6 millivolt, and greater, from several levels, followed by a small R summit, a small S, a slightly elevated RS-T segment, and a moderately inverted T wave. No satisfactory EA leads were recorded; the abnormal EV lead, however, confirmed the suspicion of posterior myocardial infarction which was aroused by the changes in the standard leads.

CASE 4.—G. L., a man, aged 43, had a typical history of coronary occlusion in October, 1938. About one month later, Dec. 1, 1938, the (four lead) electrocardiogram (Fig. 5) showed conclusively that the patient had recently had posterior myocardial infarction.

In the seventh week of the disease, esophageal Lead EV, with the electrode 52.5 cm. from the nares, showed a deep Q wave of 0.6 millivolt, followed by a smaller R wave and an S wave which was equivalent in voltage to the Q wave, an isoelectric RS-T segment, and a sharply inverted T wave. The EA leads were normal. In the tenth week of the disease, the standard precordial and esophageal leads showed definite changes, as compared with the previous tracings (Fig. 5). The persistent abnormality in esophageal Lead EV at 52.5 cm. was the presence of deep Q waves of 0.8 millivolt, with sharply inverted T waves of 0.6 millivolt. Thus, the changes in the EV lead again confirmed the impression gained from the standard leads. This patient returned to work and has no cardiac complaints.

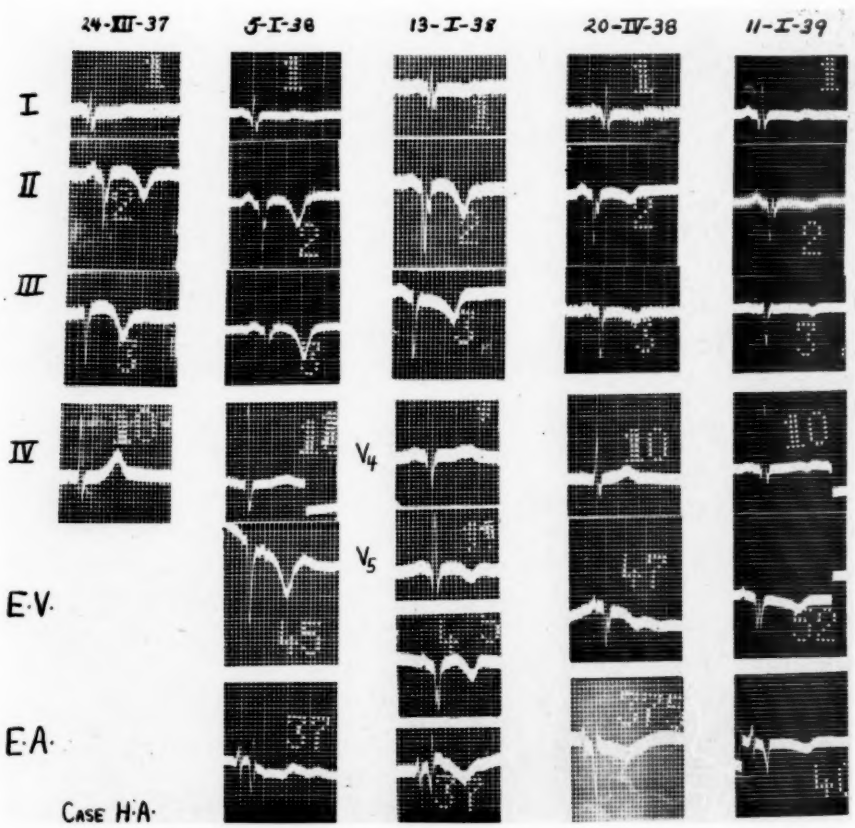

Fig. 6.—Five electrocardiograms on the same patient over a period of one year, showing progressive changes in four EV leads which are indicative of healing of a posterolateral myocardial infarct.

CASE 5.—H. A., a man, aged 58, had an atypical attack of coronary occlusion two weeks prior to admission. The final diagnosis was established on the basis of progressive changes in three routine serial electrocardiograms, in which the Q_3T_3 type of abnormality was ascribed to a posterior myocardial infarction (Fig. 6).

The abnormal, W-shaped QRS_1, with a slightly depressed $RS\text{-}T_1$ segment and a low T_1 of 0.5 millivolt, was explained by the abnormal precordial potentials from the region of the apex; these explorations suggested (Fig. 6, Jan. 13, 1938) that there was an incomplete infarction of the left lateral ventricular wall or apex.

In the fifth week of the disease (Jan. 5, 1938), esophageal Lead EV, with the electrode about 45 cm. from the incisors, showed a deep Q wave only, and a sharply inverted T wave. The EA lead was not definitely abnormal at this time or subsequently, in the course of a year. Abnormal EV potentials were found in this case in the sixth week, and in the fifth, ninth, and eleventh months after the onset of the disease (Fig. 6). All of these confirmed each other, although progressive changes had taken place, presumably because of healing of the infarcted area near the exploratory electrode. It should be noted that, in Lead EV, a persistent, abnormally deep Q wave and inverted T wave remained in this region and at lower levels over this period of time and confirmed the diagnosis of infarction of the posterior ventricular wall which was made from the standard leads.

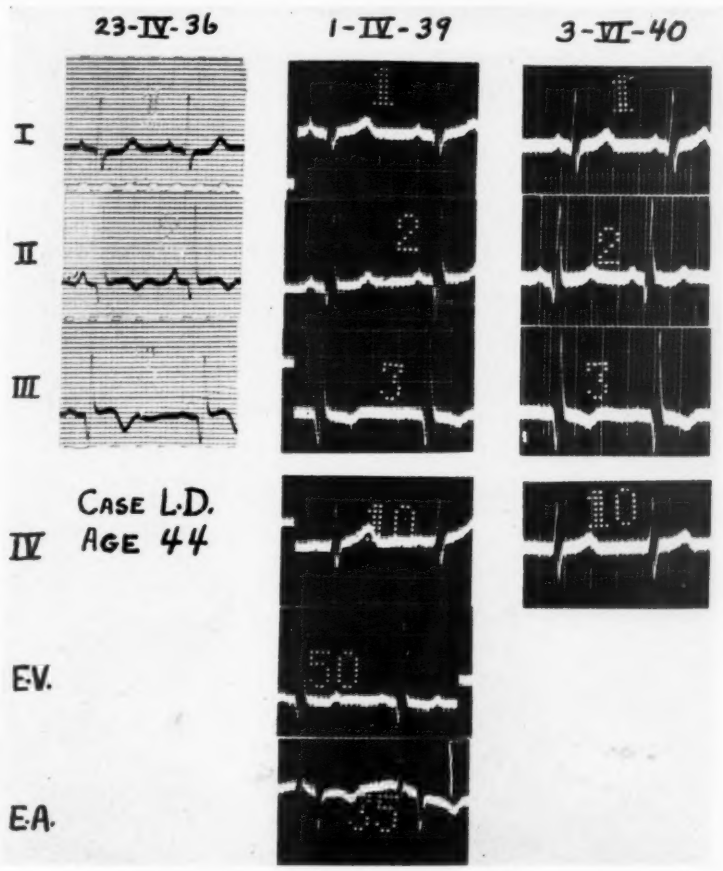

Fig. 7.—Three electrocardiograms on a patient with posterior myocardial infarction, showing progressive changes. Note that the EV lead shows an upright, electropositive T wave.

D. Healed Posterior Myocardial Infarction

CASE 1.—L. D., a man, aged 44, had an attack of coronary occlusion on April 18, 1936. The pain soon disappeared, but dyspnea on exertion continued for about three years. This was relieved by a reduction in weight. In 1940, there were no cardiac complaints. Standard electrocardiograms taken two and five days (Fig. 7) after the onset showed a Q_3T_3 pattern, with progressive changes indicating

recent posterior myocardial infarction. Studies in our laboratory, in 1939, showed a marked tendency for the T wave to return to normal. However, the deep Q_2 and Q_3 persisted. One year later, no evidence of further change in the standard leads could be detected. Lead IV was normal in 1939 and 1940.

The EV leads (Fig. 7, April 1, 1939), taken three years after the initial symptoms, showed an abnormal Q wave, 0.7 millivolt in size, or larger, from levels 45.0 to 55.0 cm. from the nares. This was associated with tall R waves and upright T waves at each level. However, the EA leads were within normal limits. It appears that in the EV leads the T waves may be upright if healing of the posterior infarct has taken place.

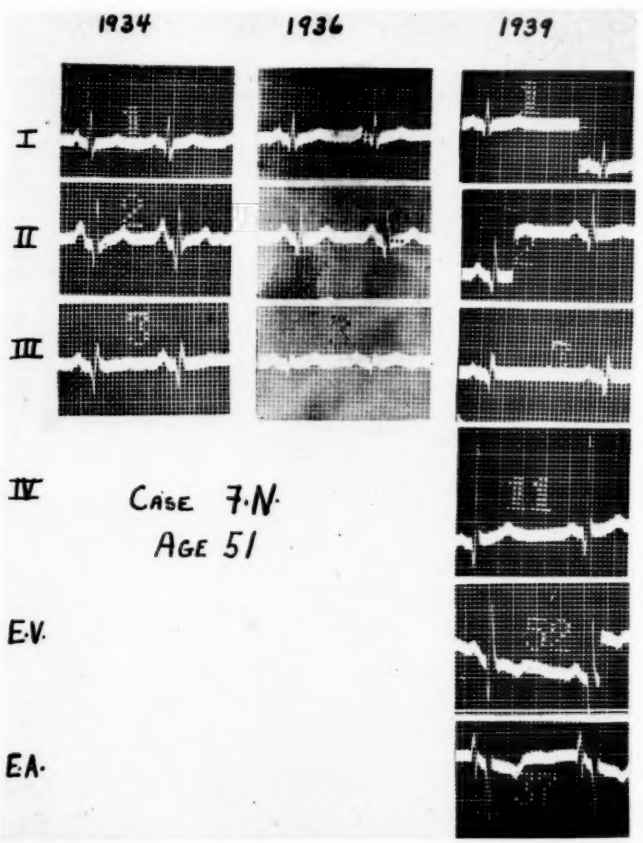

Fig. 8.—Three electrocardiograms on the same patient, showing that the EV lead is helpful in the interpretation of borderline electrocardiograms from Lead III.

CASE 2.—F. N., a man, aged 51, was first studied in the cardiac clinic in 1934, when he complained of anginal attacks which were related mainly to exertion, lasted from one minute to several hours, and had occurred intermittently during the preceding two years. The patient stated in 1939 that, three or four months prior to examination in 1934, he had had a severe attack of distressing precordial pain of twenty-four hours' duration, accompanied by a cold sweat. Morphine was required to arrest the pain. After this attack the angina had diminished considerably. Thus, clinically, he had arteriosclerotic heart disease associated with a persistent anginal syndrome, and had probably had a coronary occlusion in 1939.

In the first electrocardiograms (Fig. 8), taken in 1934 and 1936, attention was drawn to deep Q waves in Leads I, II, and III of 0.2 millivolt and greater. They were never regarded as being caused by coronary occlusion, probably because the conventional inversion of the T waves in Leads I, II, and III had not occurred in the tracings. In comparison with the 1939 tracings (Fig. 8), little change except the slight regression of the T waves in Leads I, II, and III had taken place. In the precordial series at this time, Q waves of 0.4 millivolt were present, with positive T waves in the V_5 to V_6 region. Unless additional evidence were forthcoming, these observations would be equivocal in so far as the possibility of myocardial infarction was concerned.

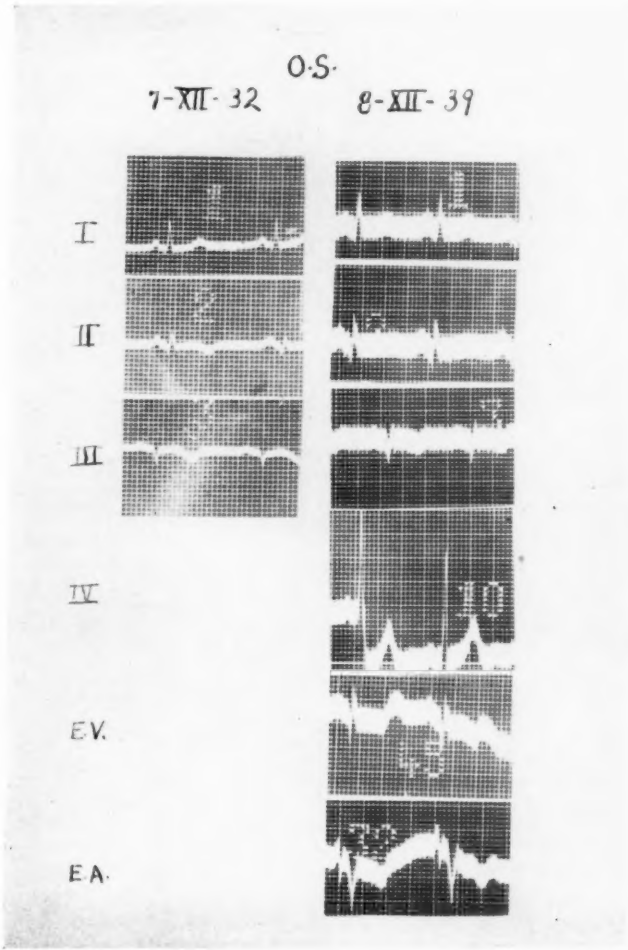

Fig. 9.—Two electrocardiograms on the same patient, showing that the EV lead and Lead IV are helpful in interpreting low voltage electrocardiograms; the patient had no complaints referable to his heart at that time.

In 1939, about five years after the onset of the disease, the EV leads from several levels were abnormal. The EV lead at 52.5 cm. (Fig. 8, 1939) showed a deep Q wave of 0.7 millivolt, associated with a slurred R wave of 1.2 millivolts and an inverted T wave of 0.13 millivolt. The EA leads were within normal limits. Thus,

myocardial infarction which was not clearly indicated by the standard leads was diagnosed by means of an abnormal esophageal electrocardiogram about five years after its occurrence.

CASE 3.—O. S., a man, aged 52, was studied in the cardiac clinic for the first time in 1932. He complained of intermittent chest pain, with radiation down the left arm, which was related to physical exertion. There was no history of an acute onset. He was well developed, somewhat obese, and weighed 190 pounds. Although he was not cooperative in the clinic, he later returned voluntarily for an electrocardiogram. At this time he no longer had angina, and was working steadily at the age of 59. He had not reduced his weight. Clinically, in 1939, the case was one of asymptomatic or healed coronary occlusion. The initial electrocardiogram (Fig 9, 1932) was of the Q_3T_3 type, with low voltage, and was typical of posterior myocardial infarction. The standard leads, in 1939, showed a persistent Q_3T_3 pattern, with T-wave changes toward a more normal direction, but of low voltage. Lead IV was within normal limits.

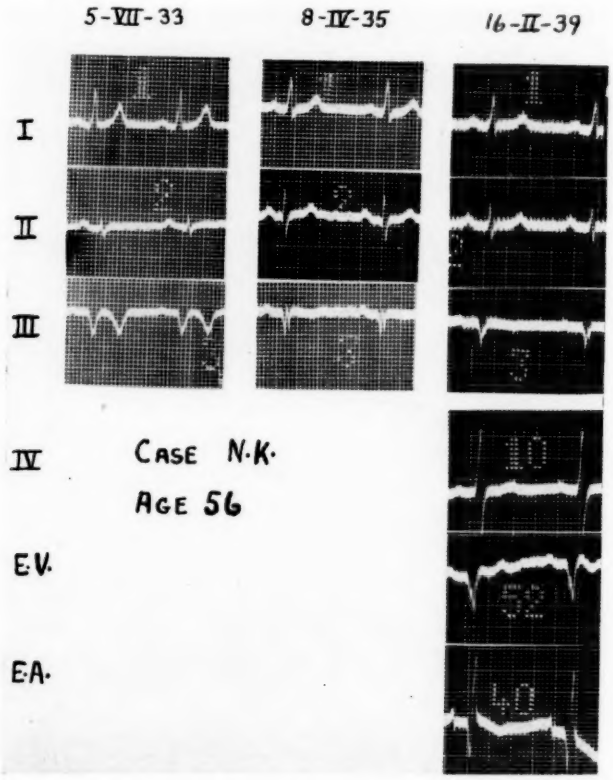

Fig. 10.—Three electrocardiograms on a patient with posterior myocardial infarction, showing an upright T wave in Lead EV in the healed stage of the disease, six years after the initial symptoms.

About seven years after the initial signs of coronary disease, the EV leads (Fig. 9) showed a Q wave of 0.7 millivolt and a diphasic T wave, which were definitely abnormal. The deep Q wave was present from 45 to 57.5 cm. from the nares, and at lower depths it was associated with an inverted T wave. The EA leads were within normal limits.

CASE 4.—N. K., a man, aged 56, suffered severe precordial distress while at work two months prior to his first clinic visit on June 29, 1933. This was not relieved by stooping over, and the patient was forced to take a taxicab home, although he had walked forty blocks to work on the same day. He remained in bed for about three months. This story, together with changing electrocardiograms (Fig 10), probably of the Q_3T_3 pattern, accompanied by low voltage of QRS_2 was, in 1933, adequate to establish a diagnosis of posterior myocardial infarction. Five years after the initial symptoms, although the patient had no complaints referable to the heart, Q_3 was still the sole QRS_3 complex; however a significant Q_2 was never present.

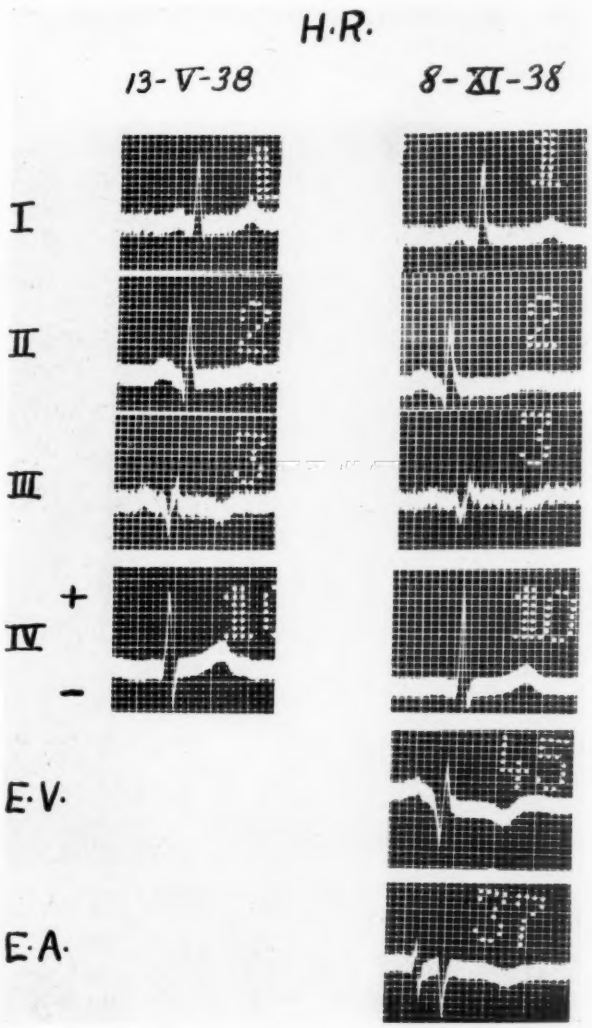

Fig. 11.—Two electrocardiograms on the same patient as in Fig. 12, showing the value of the EV lead in interpreting borderline electrocardiograms sixteen years after the initial symptoms.

The initial EV leads (Fig. 10) at several levels showed only a deep Q of 1.5 millivolts and a positive T wave. The QRS was definitely abnormal, although T was

upright but of low voltage. These abnormalities indicated a posterior wall lesion. Lead EA was within normal limits.

CASE 5 (*A Case of Equivocal Standard Leads*).—A cardiac clinic patient, H. R., a man, aged 73, was in good health in 1938, and had no complaints referable to his heart. As a matter of routine, an electrocardiogram was taken and compared with one made in 1933, which was regarded as normal in our laboratory. However, in the absence of clinical notes, the interpretation of the 1938 record (Fig. 11) stated that the Q_2 and Q_3 were difficult to evaluate, for the voltage of Q_3 was greater than one-quarter of that of R_2, while T_2 was low and T_3 inverted. Lead IV was normal, and there were no evident changes since 1933 in the standard leads.

In 1939, a history of viselike precordial pain which occurred intermittently for five or six weeks in 1922 was obtained, and it was discovered that initially his complaint had been diagnosed and treated as "influenza" by a private physician. Six weeks later he had come to the cardiac clinic, where his complaints were regarded as indicating "rheumatic fever," with symptomatic myocarditis. Pathognomonic signs of rheumatic heart disease never developed. In 1933, the cardiac diagnosis was changed to "coronary sclerosis associated with a mild anginal syndrome."

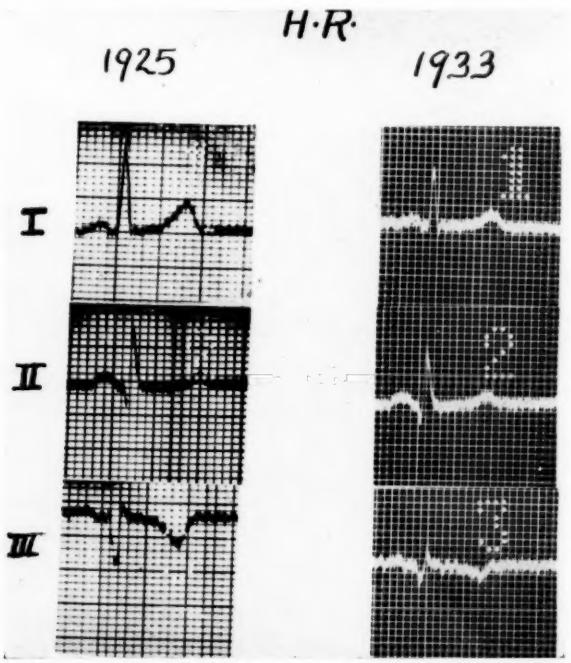

Fig. 12.—Two electrocardiograms on the same patient as in Fig. 11, confirming a late diagnosis of posterior myocardial infarction by the abnormalities in the standard leads.

This history made us skeptical of the earlier diagnosis, and, therefore, the posterior ventricular region was explored on Nov. 8, 1938 (Fig. 11). The EV leads resembled those in the above-described cases of posterior myocardial infarction, and suggested that the patient had a healed posterior myocardial infarct. Sixteen years after the onset of the disease he had a deep Q and inverted T in the EV leads. This diagnosis was later confirmed by the discovery of a deteriorated record which had been taken on this patient in 1925 (Fig. 12). Comparison with more recent tracings (1933, Fig. 12) showed that myocardial changes must have taken

place; in these the abnormal Q_2 and Q_3 were accompanied by a low, upright T_2 and an inverted T_3. Therefore, the esophageal electrocardiograms led to the specific localization of an old infarct, although the standard leads had been equivocal for the preceding five years.

E. Roentgenkymograms in Posterior Myocardial Infarction

Autopsies were not done in the case of E. E. (Fig. 2) and J. H. (Fig. 3); therefore, there was no opportunity to correlate post-mortem observations with the potentials of the EV leads in cases of posterior occlusion.

Up to the present time, no correlation is known to have been established "in vivo" between the EV lead and the roentgenkymogram in cases of posterior myocardial infarction. This was attempted in two typical cases; however, the EV leads were made with the patients recumbent, and the kymograms with the patients in the vertical position. Therefore, the true kymographic outline of the posterior heart wall may have been obscured by the lower border of the left auricle, for the latter possibly assumes a lower position because of its own weight, or becomes less distorted because it no longer lies in juxtaposition to the spine. This possibility was suggested by comparative studies (not yet reported) of the EA and EV leads in the recumbent and standing positions.

CASE 1.—In the case of G. L. (Fig. 5), which was typical of posterior myocardial infarction, as far as the standard and EV leads were concerned, there was no evidence of infarction in the left lateral kymogram at a level corresponding to 47 to 55 cm. from the nares, which was the location of the infarct, according to the esophageal leads.

CASE 2.—In the case of H. A. (Fig. 6), which was typical of posterior myocardial infarction and incomplete infarction of the left wall, as shown by the standard, precordial, and EV leads, a left lateral roentgenogram and several left oblique kymograms showed no evidence of infarction at levels corresponding to 45 cm. or more from the teeth.

In conclusion, roentgenkymographic studies in these two cases yielded nothing to support a diagnosis of posterior myocardial infarction. It is believed that better results may possibly be obtained by taking roentgenkymograms with the patient in the recumbent position. The negative results in these cases do not rule out infarction of the posterior, lateral, or diaphragmatic cardiac wall.

F. Other Factors Influencing the Initial QRS Deflections in the Esophageal Ventricular Lead

If Q is the only QRS deflection in EV leads, a diagnosis of posterior myocardial infarction is not always justified. This is illustrated by some of the following cases in which there was no evidence of coronary occlusion. The presence of an initial, small R wave in the EV leads is probably not abnormal.

CASE 1 (*Left Axis Deviation*).—H. H., a man, aged 65, had been in good health; his blood pressure was normal, but he had slight cardiac enlargement and a systolic murmur. His electrocardiogram (Fig. 13) showed left axis deviation, a low T_1, and a normal Lead IV. The EV leads from several levels showed an initial, small R wave of about 0.4 millivolt, and a much deeper S wave. These are not definitely abnormal. The EA leads were within normal limits. This study was done as a routine, not because of complaints, and indicated that caution in the interpretation of the small R wave in EV leads in some cases of axis deviation is necessary.

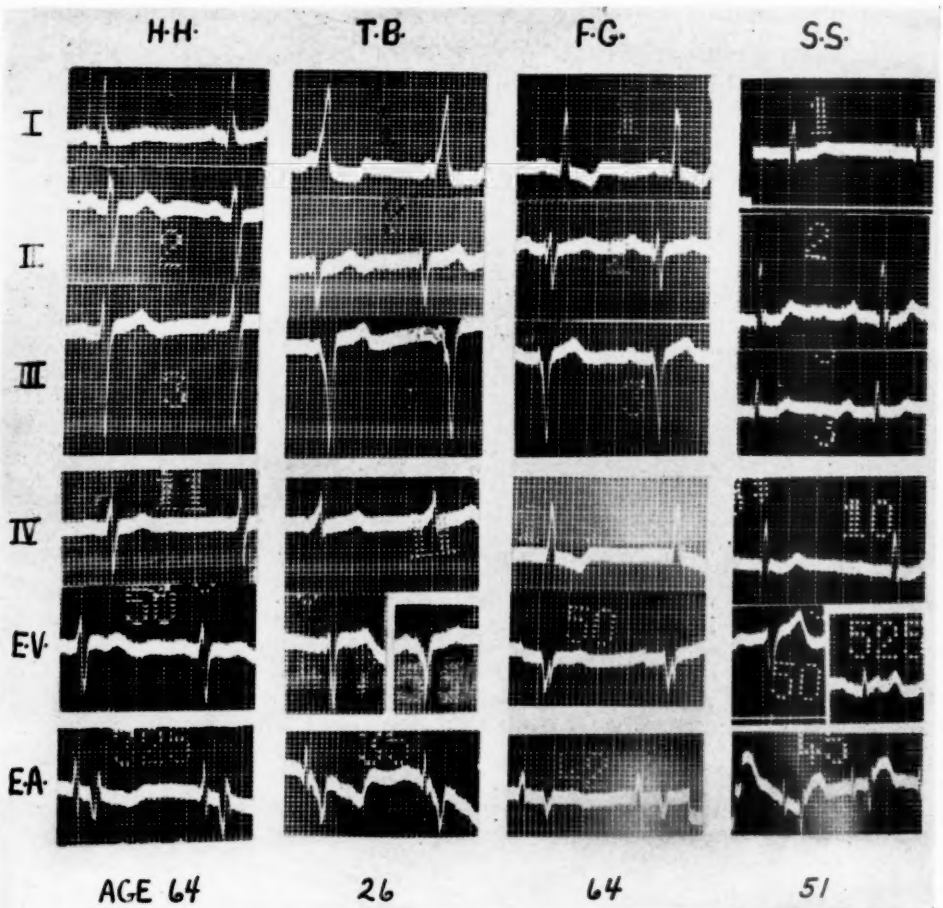

Fig. 13.—Factors influencing the appearance of the QRS complex in the EV leads of four patients, in the absence of a conclusive history or other specific signs of coronary occlusion.

CASE 2 (*Intraventricular Block With Short P-R Interval*).—T. B., a woman, aged 26, had had several short paroxysms of tachycardia during emotion or excessive physical exertion. There was no history of rheumatic fever and chorea, but she had had scarlet fever. There were many ventricular and auricular extrasystoles at the ages of 14 and 16, and murmurs were "intermittent" in childhood. A faint systolic murmur was present in 1939. No roentgenologic evidence of cardiac abnormality was found at any time.

Routine electrocardiograms (Fig. 13) showed a persistently short P-R interval (0.10 second), a prolonged QRS interval (0.12 second), QRS slurring in Leads I, II, III, and IV, marked left axis deviation, and an inverted T_1. Persistent left axis deviation and intraventricular block, with a short P-R interval, had been present in repeated tracings for the preceding eight years.

The abnormal EV leads (Fig. 13) at the lowest levels (52.5 and 55 cm. from the nares, i.e., probably subdiaphragmatic and in the stomach) showed a slurred Q wave as the sole QRS complex, followed by an isoelectric RS-T segment and upright T wave. At levels nearer the auriculoventricular border (EV, 47 cm.) a small R wave preceded the deep S wave, and was followed by an isoelectric RS-T segment and an upright T wave. The EA leads were not definitely abnormal except for the slurred Q wave, which was the only QRS complex. It was followed by an inverted T wave. In summary, what was apparently a Q wave was present in the EV lead in the absence of coronary occlusion.

CASE 3 (*Left Axis Deviation and Left Ventricular Hypertrophy Associated With Hypertension*).—F. G., a man, aged 64, who was known to have hypertensive cardiac disease, with marked left ventricular enlargement, was admitted to the hospital because of cardiac failure. The standard leads (Fig. 13) showed a QRS conduction time of 0.10 second, a P-R interval of 0.20 second, pronounced left axis deviation, inversion of T_1, and a bizarre QRS_2. The precordial lead showed T-wave inversion in the apical region, whereas QRS_4 was essentially normal.

The abnormal EV leads (Fig. 13, F. G.) showed an initial R wave of about 0.05 millivolt, followed by a notched S wave of 1.2 millivolts, an isoelectric RS-T segment, and a T wave of 0.1 millivolt. The EA lead showed an M-shaped QRS complex, followed by a diphasic T wave. Digitalis may have been responsible for part of the T-wave abnormalities. No known abnormalities indicative of coronary thrombosis were present in this case at any time; however, the QRS complex was abnormal in the EV leads. The position and size of the heart may have been responsible for the difference between QRS in the EV leads and QRS_4.

CASE 4 (*Questionable Coronary Occlusion*).—S. S., a retired business man, aged 55, gave an unreliable history which was similar to that of coronary occlusion; it began three years before admission, and continued as an "anginal syndrome" intermittently. On admission there were changes in the standard and precordial leads which suggested a toxic factor, such as digitalis, rather than primary myocardial disease. The patient denied having taken this drug. After ten days of rest in bed and withdrawal of all known cardiac medications, except as prescribed, the standard and precordial leads became essentially normal and resembled those taken elsewhere a few years earlier. After he had been digitalized with 15 grains of digifolin, the curves became abnormal and resembled those taken on admission. Therefore, it was felt that the patient was a malingerer. The patient was twice admitted elsewhere after discharge from our hospital. The opinions held were that the electrocardiograms were abnormal probably because of medication with digitalis-like drugs.

The EV leads (Fig. 13, S. S.), 52.5 and 55.0 cm. from the nares, showed no evidence of a Q wave. An R wave of 0.7 millivolt was the initial deflection and was followed by an S of 0.1 millivolt and a notched, upright T wave. The leads at 50 and 47 cm. showed an initial R wave of 0.2 millivolt, followed by a deep S wave of 3.0 millivolts and an upright T wave of 1.0 millivolt. These were normal for the EV lead within 5 cm. of the lower border of the auricle, as judged by the EA lead. The patient was in a semirecumbent position when the esophageal leads were taken.

The EA leads were obtained at the low level of 45.0 cm. and had elevated RS-T segments, with upright or diphasic T waves, presumably because of a toxic factor. The effect of digitalis on the EV lead was somewhat uncertain, for the T wave remained upright at all levels. In summary, no evidence of localized myocardial infarction was obtained by the routine, extremity, precordial, and esophageal leads in this case of what was probably malingering.

G. Other Factors Which Simultaneously Influence the Direction of the T Wave of the Esophageal Ventricular Leads and Precordial Ventricular Leads

Greater skepticism has arisen over inverted T waves than over the Q waves in the diagnosis of myocardial disease. A unimural left ventricular appearance of inverted T waves might be suggestive of a localized lesion. Adults normally have positive T waves in the apical and posterior ventricular leads. In the following cases, inversion of the T wave in leads from the apical and posterior ventricular regions occurred in the absence of QRS abnormalities in these leads. There was no conclusive history or objective indication of old or recent coronary occlusion in these cases.

CASE 1 (*Hypertensive Heart Disease With Left Ventricular Enlargement and Left Axis Deviation*).—S. L., a man, aged 36, probably had Cushing's syndrome. Chronic glomerulonephritis, multiple furunculosis, and hypertensive heart disease with a blood pressure ranging from 186/120 to 240/160 were known to have been present for one year. He had an elongated type of heart, with "25 per cent enlargement of the ventricles," and staphylococcus bacteremia. There was no history of coronary occlusion, and digitalis had not been given.

The standard leads (Fig. 14, S. L.) showed high voltage of the QRS deflections, left axis deviation, and a poorly defined, low, and diphasic T_1, T_2, and T_3. Lead IV showed a normal QRS, and abnormal, minus-plus, diphasic, low voltage T waves. The EV lead showed a normal QRS, and an abnormal, inverted T of 0.2 millivolt. The EA potentials were normal. In summary, T-wave inversion was significant in leads from the left ventricle in this case.

CASE 2 (*Hypertensive Heart Disease With Left Ventricular Enlargement and a Normal Electrical Axis*).—S. E., a man, aged 46, complained of dyspnea on exertion, a localized precordial pain, and nocturia following an upper respiratory infection. No significant improvement had occurred during the preceding three years, during which time his blood pressure ranged from 170/90 to 210/110. The pulse rate averaged 80 beats per minute, the aortic second sound was accentuated, and there were no murmurs. Roentgenologic examination showed moderate enlargement of the left and right ventricles and a widened aortic arch. Urinalysis was negative. There was nothing to suggest that coronary occlusion had occurred, and the patient had not had congestive heart failure or taken digitalis.

The abnormalities in the standard leads (Fig. 14, S. E.) were confined to the diphasic T_1 and moderately inverted T_2 and T_3. Lead IV and Lead EV were essentially the same, with small Q waves of 0.3 to 0.4 millivolt, R waves of 2.0 millivolts, and moderate inversion of the T waves. An S wave was present in Lead IV but not in the EV leads. The slightly depressed RS-T segments and moderately inverted T waves were found bimurally over the left ventricle. The EA potentials were not abnormal.

CASE 3 (*Left Bundle Branch Block in Arteriosclerotic Heart Disease*).—A. G., a man, aged 69, was hospitalized for six weeks because of an acute complaint suggesting coronary occlusion on the day of admission. The blood pressure was not abnormal. The left ventricle was slightly enlarged fluoroscopically; no murmurs were present.

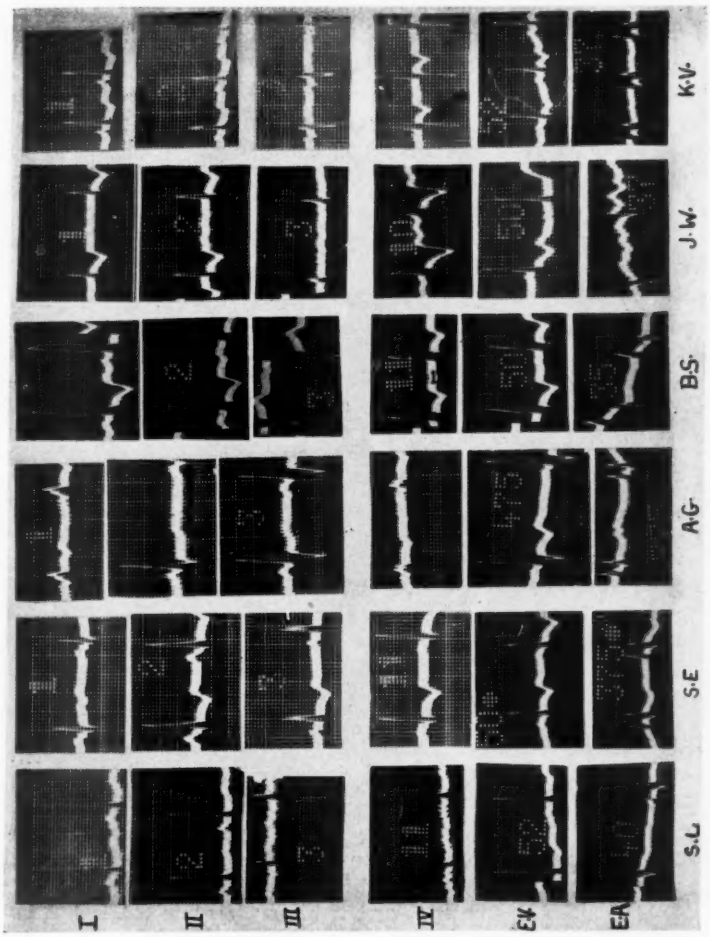

Fig. 14.—Factors which produce a bimural inversion of T waves, as detected by the EV lead and Lead IV in six different cases.

The standard leads (Fig. 14, A. G.) showed left bundle branch block, with a QRS interval of 0.12 second. Lead IV showed a low, notched R wave of 0.5 millivolt and an inverted T wave in the V_5-V_6 region. Lead EV showed a tall, notched R of 3.0 millivolts, with an inverted T of 0.5 millivolt. Lead EA showed diphasic T waves. No abnormal Q waves were present in Lead IV or Lead EV.

CASE 4 (*Left Axis Deviation and Left Ventricular Hypertrophy, With Aortic Stenosis*).—B. S., a man, aged 42, had been admitted several times because of a severe anginal syndrome, associated with rheumatic aortic stenosis, which developed late in life. Marked left ventricular hypertrophy was found fluoroscopically, and there was a palpable thrill over the aortic area. The pulse pressure was low, and the systolic level was consistent with the diagnosis. Six months before death the patient had a hemiplegia, but no evidence of myocardial infarction developed clinically. No autopsy was obtained.

The standard leads (Fig. 14, B. S.) showed high voltage of the QRS deflections, moderate left axis deviation, a QRS interval of 0.10 second, and inverted T_1 and T_2. Leads IV and EV were very similar; both had R waves of about 3.0 millivolts, followed by small S waves and inverted T waves. Lead EA showed a diphasic T wave. In summary, T-wave inversion was again common to Lead IV and Lead EV over the left ventricle.

CASE 5 (*Toxic Factors, Including Digitalis*).—J. W., a woman, aged 63, had a positive blood Wassermann reaction, mitral stenosis, an enlarged heart, and auricular fibrillation with supraventricular tachycardia before she was first digitalized. She was later given Lugol's solution because of hyperthyroidism. There was no history of coronary occlusion.

The standard lead electrocardiogram (Fig. 14, J. W.) showed normal voltage of QRS and a normal electrical axis; T_1 and T_2 were abnormally inverted, presumably because of multiple factors. Chronic auricular fibrillation was also present; the ventricular rate had slowed before this special study.

The QRS groups in Lead IV and Lead EV were within normal limits. Inverted T waves were present anteriorly and posteriorly on the left (V_4-V_6 region), and at all levels in the EV leads (Fig. 13, J. W.). The EA lead showed a normal QRS group and a positive T wave. Although the etiology of the alteration in the T waves was doubtful, there was no reason for ascribing inversion of T_4 and of T in Lead EV to coronary occlusion in this case.

CASE 6 (*Effects of Nutritional Deficiency, Superimposed on Probable Arteriosclerotic Heart Disease*).—K. V., a woman, aged 74, was admitted in a semicomatose state and remained psychotic for about six weeks, whereupon, with the administration of large doses of vitamin B, the psychosis disappeared within three days' time. Coronary occlusion was suspected initially, but conclusive indications of infarction never developed in the four routine leads. The rapid pulse rate slowed; the transverse diameter of the markedly enlarged heart decreased about 3 cm.; the pulmonary congestion cleared up; the peripheral edema over the arms, legs, and back disappeared; and the enlarged liver shrank until it was no longer palpable. Meanwhile, the blood pressure fluctuated from normal to high, and the loud, apical, mitral systolic murmur remained unchanged by the vitamin B therapy. The left ventricle was moderately enlarged, and the heart was of the elongated type as shown by fluoroscopic examination.

The standard lead electrocardiogram (Fig. 14, K. V.) showed normal conduction, slight left axis deviation, moderate inversion of T_1 and T_2, and deep inversion of T_4. Four weeks after admission, T_3 became slightly inverted. With the administration of vitamins B_1 and B_2, T_1 and T_2 became less inverted, and T_3 became upright again. Lead IV and lead EV showed normal QRS groups; however, inverted T waves were present in the V_4-V_6 region and in esophageal leads from the left ventricular region. The EA leads showed normal QRS and isoelectric T waves. Thus, it appears that, when myocardial disease involves an enlarged left ventricle, it is not unusual to observe inverted T waves anteriorly and posteriorly.

DISCUSSION AND CORRELATION

The exploratory leads used in this study were essentially unipolar with respect to a central, indifferent terminal. The changes of potential represented by the normal precordial leads were indicated by Lead IV in D. B., E. G., D. K. (Fig. 1), and R. W. (Fig. 2). These curves were similar to each other in most respects, and also very similar to normal

posterior ventricular leads (EV) in these same cases. Therefore, one may conclude that indirect exploratory leads from the normal anterior or posterior walls were similar in outline[9, 10] with respect to the P wave, QRS, and T waves, regardless of whether the chest or the retrocardiac tissue separated the electrode from the normal left ventricle.

The indirect EA leads from the normal left auricle in these same cases (D. B., E. G., D. K., R. W.) showed diphasic P waves, with auricular intrinsic waves which identified the auricular level. In general, the characteristic QRST deflections appeared to be inverted images of those in exploratory leads from the left ventricle (EV and IV). The QRST waves in the EA leads also closely resembled those recorded by Wilson and his associates directly from the left ventricular cavity in experimental animals. Thus, in normal EA leads, the blood pool of the heart appeared to be the physical medium and the most direct path of conduction of the action currents produced by the ventricle. It is also responsible for conducting these currents away from the ventricular cavity to the auricular surface during the ventricular electrical cycle; this accounts for the typical form of the QRST complex (in the EA lead), which is the inverted image of the electrocardiogram obtained from the normal surface of the left ventricle. Other exploratory electrocardiograms on normal subjects, taken above the base of the heart, e.g., an esophageal lead opposite the aortic arch, or a unipolar lead of the right arm[16] (using Wilson's central terminal as the indifferent electrode), are similar in form to the QRST complex in the EA lead. When apparently marked and gross abnormalities occur in myocardial infarction (cases B. C. and E. E., Fig. 2), the EA electrocardiogram and other exploratory electrocardiograms (not included in this paper) above the base of the ventricle are greatly altered from the normal potential found in these regions.

A deep Q wave occurred as the sole QRS complex in EV leads in three cases of posterior coronary occlusion, namely J. H. (Fig. 3), H. A. (Fig. 6), and N. K. (Fig. 10); these leads closely resembled precordial Lead IV in the case of anterior occlusion, B. C. (Fig. 2), and the EA lead of normal subject D. K. (Fig. 1). It appears that the common factor which produced similar QRS outlines[9] was the large, inert mass of dead muscle in the infarct cases and the large pool of blood which electrically connected and effectively short-circuited the auricle and ventricle to the EA lead of the normal subject. Thus, both conduction paths, although they were technically different, actually permitted a recording of the action current variations from the ventricular cavity.

EV leads from the posterior myocardial infarct regions in which Q was not the sole QRS complex were obtained in seven cases, namely, E. E. (Fig. 2), L. B. (Fig. 4), C. L. (Fig. 5), L. D. (Fig. 7), F. N. (Fig. 8), O. S. (Fig. 9), and H. R. (Fig. 11). These deflections resembled the QRS group in EA leads from normal subjects D. B. (Fig. 1),

E. G. (Fig. 1), and R. W. (Fig. 2), and also the exploratory leads from the margins of experimental infarcts obtained by Wilson and his associates. Thus, it appeared that the EV leads in these cases were probably taken over areas in which the infarction did not involve all of the muscle under the electrode, rather than over the center of areas of complete infarction. These observations were, nevertheless, helpful in locating the lesion in the acute, subacute, and chronic stages of myocardial infarction, ranging from one day to sixteen years after the onset of the disease.

Significant RS-T segment elevation in EV leads occurred in only two cases of acute posterior infarction, namely, E. E. (Fig. 2) and L. B. (Fig. 4). Significant RS-T deviations in EV leads were not noted in the subacute or chronic stages of posterior myocardial infarction. A slight RS-T (Lead EV) segment depression occurred in the case of anterior occlusion, B. C. (Fig. 2). Wood and Wolferth[6] and Wilson, et al.,[3, 12] have shown that RS-T segment (Fig. 2) deviations disappear in a few hours from exploratory leads taken directly over cardiac infarcts produced in animal experiments. They also showed that, in direct leads from the side of the heart opposite the injured region, the RS-T displacement was electronegative, and, from the same side as the injury, electropositive. This is confirmed by the above observation in the EV lead for the RS-T segment is depressed (electronegative) in acute anterior myocardial infarction (B. C., Fig. 2) and elevated (electropositive) in acute posterior myocardial infarction (E. E., Fig. 2). In regard to T waves in the EV leads in cases of posterior occlusion, variable results were observed. In all of five cases of recent posterior occlusion, namely, E. E. (Fig. 2), J. H. (Fig. 3), L. B. (Fig. 4), G. L. (Fig. 5), and H. A. (Fig. 6), the T waves in EV leads were inverted. In three of five cases of old or healed lesions, namely, F. N. (Fig. 8), O. S. (Fig. 9), and H. R. (Fig. 11), the T waves were also inverted or diphasic; however, in two cases, namely, L. D. (Fig. 7) and N. K. (Fig. 10), the T waves were upright. The T wave remained electropositive in the case of anterior occlusion, B. C. (Fig. 2). Therefore, in general one may conclude, with regard to the QRST deflections in EV leads in cases of posterior myocardial infarction, that the deep Q wave, if present and abnormal, tends to persist for years, whereas the T waves, if inverted and abnormal, may remain inverted, or may become diphasic and upright during the process of healing. The RS-T segment elevation is transient, and it is significant only in some cases of acute posterior infarction. These deviations, if found together in the EV lead, are as specific indications of posterior myocardial infarction as similar deviations in Lead IV are of anterior myocardial infarction.[13]

Less specific signs of posterior myocardial infarction in EV leads, such as inversion of T while QRS and QRST remain essentially normal,

might occur with equal frequency in other types of myocardial disease, or in cases in which the infarct is small; however, if these changes suggest a localized myocardial lesion, they may be an aid in reaching a correct interpretation[14] of the observed variations.

Some of the factors which were found to modify or produce abnormal QRS waves in EV leads were having the patient upright while recording, marked enlargement of the left auricle (not described in this paper), left axis deviation (Fig. 13, H. H.), intraventricular block with a short P-R interval (Fig. 13, T. B.), and marked left ventricular hypertrophy (Fig. 13, F. G.). Some of the factors which were found to modify, and tended simultaneously to invert, the T waves of the EV lead and Lead IV (V_4-V_6) were extensive infarction, probably involving the posterior and lateral walls (Fig. 4, L. B., and Fig. 6, H. A.), multiple infarctions (not described in this paper), left ventricular enlargement caused by various diseases, such as hypertension (Fig. 14, S. L. and S. E.), left bundle branch block (Fig. 14, A. G.), aortic stenosis (Fig. 14, B. S.) and toxic or nutritional diseases of the myocardium (Fig. 14, J. W. and K. V.).

Our ability to differentiate myocardial lesions accurately is increased by the use of multiple precordial and multiple esophageal leads in conjunction with the standard leads, together with a knowledge of the clinical phenomena in a given case. Until the technique is much improved, roentgenkymography will be of little value in confirming a diagnosis of posterior myocardial infarction in the subacute or chronic stage of the disease.

The EV lead is of greatest value in interpreting doubtful changes in QRS_3, and occasionally in QRS_2, as illustrated in L. B. (Fig. 4, Feb. 23, 1940), F. N. (Fig. 8, 1934, 1936, and 1939), O. S. (Fig. 9, Dec. 8, 1939), N. K. (Fig. 10, 1935, 1939), and H. R. (Fig. 12, 1933, and Fig. 11, 1938). In each of these instances positive information concerning the presence of posterior myocardial disease was obtained by the EV lead.

The greatest value of the EA lead is in the study of auricular arrhythmias, as shown by Brown,[8] in 1936, and more recently by Nyboer and Hamilton.[15] The presence or absence of auricular intrinsic deflections in the P waves of juxta-auricular leads from the esophagus has been a valuable index of the anatomic relation of the electrode to the posterior part of the heart, and has made it possible to ascertain with greater accuracy the potentials of ventricular levels in normal subjects and patients with heart disease. Although the QRST complexes from the esophageal auricular leads in normal subjects have fixed patterns, the interpretation of abnormalities in these leads is still very difficult. In the cases reported herein, the T wave in EA leads was inverted, diphasic, upright, or nearly isoelectric in various forms of myocardial disease; however, the normal T waves in EA leads were inverted (Fig.

1). At present, the cause and significance of the major changes in the form of the QRST complexes of the esophageal auricular electrocardiograms are not fully understood.

SUMMARY

1. The standard leads, a selected precordial lead (IV), and selected esophageal leads from the ventricular (EV) and auricular (EA) levels were taken on four normal subjects, in one case of anterior infarction, and in ten cases of posterior myocardial infarction.

2. Similar studies were made on ten other patients who had a history, physical signs, or something else to suggest myocardial disease, in order to differentiate the abnormalities which they presented from the more specific electrocardiographic indications of coronary occlusion.

3. Study of two typical cases of posterior myocardial infarction by means of the roentgenkymograph yielded no information.

4. The esophageal ventricular electrocardiograms which were characteristic of posterior myocardial infarction closely resembled precordial electrocardiograms which were characteristic of anterior myocardial infarction, and vice versa.

5. In some cases in which the standard lead electrocardiograms were equivocal, a definite diagnosis of posterior myocardial infarction was made by means of the esophageal juxtaventricular leads.

6. The ventricular complex of the esophageal juxta-auricular electrocardiogram was often found to be altered in cases of myocardial disease.

CONCLUSION

Our knowledge of the complex electrical field of the heart will never be complete until the diseases of the human myocardium are studied by indirect electrical explorations of the posterior, lateral, and anterior walls of the ventricles and of the right and left auricles, as well as by the standard lead electrocardiogram. Specific and helpful knowledge regarding the form of the electrocardiogram opposite the ventricle posteriorly was obtained with an esophageal lead in many cases of posterior myocardial infarction, whether acute or chronic.

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OBJECTIVE EVIDENCE OF THE EFFICACY OF MEDICINAL THERAPY IN ANGINA PECTORIS

A. Stone Freedberg, M.D., Joseph E. F. Riseman, M.D., and Erwin D. Spiegl, M.D.
Boston, Mass.

IN THE treatment of patients with angina pectoris some form of medication is usually prescribed, but in the selection of such drugs the physician must rely either on clinical impressions of their therapeutic value or on the unsupported claims of the manufacturers. Many attempts to prove the value of medication have been made, but there has been little objective evidence of therapeutic action. As a result, the Council of Pharmacy and Chemistry of the American Medical Association, in 1937,[1] in reviewing the claims for the therapeutic efficacy of xanthine derivatives, reversed their decision of 1930,[2] and "decided that there is no warrant for claims of efficacy as a dilator of the coronary arteries or of usefulness in overcoming pain in coronary occlusion or angina pectoris." The purpose of the present investigation is to review the literature and present objective evidence of the pharmacodynamic action of drugs under conditions comparable to those commonly used in the treatment of angina pectoris.

REVIEW OF THE LITERATURE

Experiments on Laboratory Animals

Experiments on laboratory animals have been carried out to ascertain the effect of drugs on the coronary arterial blood flow (Table I). Such studies include measurements of the caliber of isolated arterial rings, and measurements of the coronary blood flow in isolated, perfused hearts, in heart-lung preparations, and in intact animals (as indicated by a stromuhr or by the venous return through the coronary sinus). Despite unavoidable differences in technique and differences in the animals used, the results are extraordinarily consistent and indicate that the nitrites and purines cause coronary vasodilatation and an increased coronary blood flow, and that digitalis usually has the opposite effect. There are definite objections to these studies, however, for the results obtained under artificial conditions in normal animals are

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not necessarily applicable to coronary artery disease in man; furthermore, it is difficult to ascertain whether the concentrations of the drugs used in these experiments were comparable to what might be present in the circulating blood of patients taking such drugs.

The effect of drugs on the collateral circulation has been studied after experimental occlusion of a main coronary artery, but conflicting results have been obtained (Table I). The pathologic anatomy and physiology of acute experimental coronary occlusion are not comparable, however, to those of angina pectoris as it is seen clinically. As Schlesinger, Blumgart, and their coworkers[3, 4] have shown, an anastomotic circulation may not develop following *acute coronary occlusion,* whereas the hearts of the patients with angina pectoris possess a rich, functioning collateral circulation, presumably as a result of *chronic narrowing* of the main coronary arteries.

Studies on Patients With Angina Pectoris

Clinical Observations and Impressions.—The number of clinical reports which indicate that the purines are of value in the treatment of angina pectoris is too large to list; certain results and methods of study, however, deserve mention. Askanazy[5] administered theobromine sodium salicylate to patients for three weeks, alternating with similar periods without medication. His results may be translated as follows: "With the certainty (Sicherheit) of an experiment the attacks disappeared at once, or very soon after the administration of theobromine, and recurred as soon as the drug was stopped." Gilbert and Kerr[6] obtained similar results with theobromine sodium acetate in thirty-seven of sixty-nine patients; twenty showed no response to this drug. Smith, Rathe, and Paul,[7] using theophylline, found "that in a fairly large percentage favorable results were shown . . . . increases in dosage helped patients in whom the results of the medication had been in doubt."

Controlled Clinical Observations.—In 1933, Evans and Hoyle[8] reported the results of two and one-half years of observation on ninety patients with angina who were given various types of medication alternating with a placebo, and who kept a careful record of their attacks. They found "that a measure of improvement appears to result from every remedy tried, and at least as great an improvement appears during treatment with placebo . . . . we have been unable to convince ourselves that any drug tested is worthy of trial in the routine treatment of the disease." Master, et al.,[9, 10] and Gold, Kwit, and Otto[11] corroborated these observations; the latter stated "that patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine

TABLE I

SUMMARY OF EXPERIMENTAL STUDIES ON THE EFFECT OF DRUGS ON THE CORONARY BLOOD FLOW

DRUGS USED	MEASUREMENT OF DIAMETER OF ISOLATED RINGS OF CORONARY ARTERIES IMMERSED IN PHYSIOLOGIC SOLUTIONS TO WHICH DRUGS HAVE BEEN ADDED[a]			MEASUREMENT OF CORONARY BLOOD FLOW IN HEART-LUNG PREPARATIONS OR ISOLATED, PERFUSED HEARTS[a]			MEASUREMENT OF CORONARY BLOOD FLOW IN INTACT ANIMALS		
	CORONARY ARTERY DILATATION	CORONARY ARTERY CONSTRICTION	NO EFFECT	CORONARY FLOW: INCREASED	CORONARY FLOW: DECREASED	NO EFFECT	CORONARY FLOW: INCREASED	CORONARY FLOW: DECREASED	NO EFFECT
Nitrites									
Nitroglycerin	Voegtlin et al.[37]			Katz et al.[56, 57] Smith et al.[58]			LeRoy[65] Meyer[85] Schloss[87] Wégria[88] Essex et al.[89, 90]	Bond[86]	
Amyl nitrite	Cow[38] Loeper et al.[39] Voegtlin et al.[37] Pal[40]			Loeb[59] Bodo[60] Krawkow[47]			Francois-Frank[91] Essex et al.[90] Meyer[85] Schloss[87] Wégria[88]	Bond[86]	
Octyl nitrite	Krantz et al.[41]			Krantz et al.[41]			Krantz et al.[41]		
Sodium nitrite	Voegtlin and Macht[37] Loeper et al.[39] Kountz,[42] Cow[38] Eppinger and Hess[43] Pal[40]			Katz et al.[56, 57] Bodo,[60] Kountz and Smith[61] Kountz,[42] Wedd[62] Fowler et al.[63]			Schloss[87]		
Purines									
Theobromine	Pal[40] Eppinger and Hess[43]		Voegtlin and Macht[37]	Loeb[59] Heathecote[64] Kountz and Smith[61] LeRoy[65] Krawkow[47, 66] Woichansky[67]			Smith and Miller[92] LeRoy[65] Gilbert and Fenn[93]		Bond[86]
Theobromine sodium salicylate				Smith et al.[58] Kountz and Smith[61] Heathecote[64] Woichansky[67]			Sakai and Saneyoshi[94] Gilbert and Fenn[93]		
Theobromine sodium acetate				Fowler et al.[63]			Gilbert and Fenn[93]		

Theophyllin				Katz et al.[56] Smith et al.[58] Guggenheimer and Sassa[68] Kountz and Smith[61] Fisher et al.[69] Heathecote[64]			Smith and Miller[92] Gilbert and Fenn[93]		
Theophyllin sodium acetate				Heathecote[64] Iwai and Sassa[70] Fowler et al.[63]			Gilbert and Fenn[93]		
Theophyllin ethylene-diamine[E]				Katz et al.[56] Smith et al.[58] Fowler et al.[63] Kountz and Smith[61] Fisher et al.[69] LeRoy[65] Guggenheimer and Sassa[68] Wedd[62] Stoland et al.[71] Iwai and Sassa[70]		Davis[72]	LeRoy[65] Gilbert and Fenn[93] Stoland et al.[71] Essex et al.[59] Wégria et al.[88]		
Caffein	Kountz[42] Eppinger and Hess[43] Voegtlin and Macht[37] Pal[40]			Katz et al.[56] Loeb[59] Kountz[42] Heathecote [64] Anrep and Stacy[75] Bodo[60] Kountz and Smith[61] Fowler et al.[63] Anitschkow[74] Hedbom[75] Iwai and Sassa[70] Krawkow[47, 66] Guggenheimer and Sassa[68] Woichansky[67]		Smith et al.[58]	Sakai and Saneyoshi[94] Meyer[85] Gilbert and Fenn[93]		Bond[86] Gilbert and Fenn[93]
Digitalis Bodies									
Digitalis[F]	Cow[38] Voegtlin and Macht[37]	Eppinger and Hess[43] Voegtlin and Macht[37]		Bodo[60] Kountz and Smith[61, D] Hedbom[75]	Loeb[59] Kountz and Smith[61, C] Wesse[77] Katz et al.[56] Deneke and Adams[76] Rabe[78]		Meyer[85]	Wesse[77] Gilbert and Fenn[95] Fenn and Gilbert[96]	Essex et al.[97] Bond[86] Wesse[77]
Strophanthin	Mikuliczish[44]	Eppinger and Hess[43]	Voegtlin and Macht[37]	Bodo[60]	Rabe[78]	Loeb[59] Fisher et al.[69]	Meyer[85]		Bond[86] Sakai and Saneyoshi[94]

TABLE I—CONT'D

DRUGS USED	MEASUREMENT OF DIAMETER OF ISOLATED RINGS OF CORONARY ARTERIES IMMERSED IN PHYSIOLOGIC SOLUTIONS TO WHICH DRUGS HAVE BEEN ADDED*			MEASUREMENT OF CORONARY BLOOD FLOW IN HEART-LUNG PREPARATIONS OR ISOLATED, PERFUSED HEARTS*			MEASUREMENT OF CORONARY BLOOD FLOW IN INTACT ANIMALS		
	CORONARY ARTERY DILATATION	CORONARY ARTERY CONSTRICTION	NO EFFECT	CORONARY FLOW		NO EFFECT	CORONARY FLOW		NO EFFECT
				INCREASED	DECREASED		INCREASED	DECREASED	
Miscellaneous (A)									
Sodium acetate							Gilbert and Fenn[93]		
Ethylenediamine hydrochloride				Guggenheimer and Sassa[68] Iwai and Sassa[70]					
Quinidine and quinine		Krawkow[47]	Kountz[42]	Hedbom[75] Starr[79]	Bodo[60]	Bodo[60] Kountz[42] Rabe[78]			
Histamine(G)	Kountz[42]	Barbour[48] Anrep[49] Rothlin[50] Kountz[42] Cruickshank and Subba-Rau[46]	Gunn[56]	Katz et al.[56, 57] Narayana[80] Kountz and Smith[61, C] Kountz[42] Müller et al.[81]	Kountz and Smith[61, D] Krawkow[47, 66]		Gunn[55] Rühl[98] Sumbal[99] Wégria et al.[88]	Dale and Laidlaw[100] Viotti[101] Feldberg and Shilf[102] Gunn[55]	
Acetylcholine		Wedd[62] Eppinger and Hess[43] Lange[45]		Narayana[80] Katz et al.[56, 57]	Wedd and Fenn[51] Katz et al.[57]	Narayana[80]	Sumbal[99] Essex et al.[89]		
Tissue extracts[B]	Lange[45]			Lange[45] Kountz and Smith[61] Fisher et al.[60] Frey and Kraut[53] Haberlandt[54] Wedd[51, 62]			Essex et al.[89]		
Adrenalin	Cruickshank and SubbaRau[46] Cow,[38] Kountz[42] Eppinger and Hess[43] Pal[40]	Kountz[42] Meyer[52]		Anrep and Stacy[73] Krawkow[47, 66] LeRoy[65] Katz et al.[56, 57] Kountz and Smith[61, D]	Katz et al.[57] Kountz and Smith[61, C] Anitschkow[74]		LeRoy[65] Bond[86] Essex et al.[89] Wégria et al.[88]		
Posterior pituitary preparations	Cow,[38] Kountz[42]	Cow,[38] Pal[40, 53, 54]			Bodo[60] Kountz[42] Anrep and Stacy[73] Narayana[80] Katz et al.[56, 57] Wedd[62]		Sumbal[99]	LeRoy[65] Essex et al.[89] Gunn[55] Wégria et al.[88]	

TABLE I—CONT'D

DRUGS USED	STUDIES OF EFFECT OF DRUGS ON COLLATERAL CORONARY CIRCULATION OF ANIMALS FOLLOWING ACUTE EXPERIMENTAL OCCLUSION OF MAIN CORONARY ARTERY										MISCELLANEOUS STUDIES
	SIZE OF INFARCT		INTENSITY OF CYANOSIS		ABILITY OF INVOLVED AREA TO CONTRACT		CORONARY BLOOD FLOW		ELECTROCARDIOGRAPHIC CHANGES		PREVENTION OF ELECTROCARDIOGRAPHIC CHANGES INDUCED BY ADRENALIN
	SMALLER	NO CHANGE	DECREASED	NO CHANGE	RESTORED	NOT RESTORED	INCREASED	UNCHANGED	REVERSED	NOT REVERSED	
Nitrites											
Nitroglycerin			Smith[109]								Douglas et al.[108]
Amyl nitrite						Wiggers and Greene[107]					
Octyl nitrite											
Sodium nitrite						Wiggers and Greene[107]		Wiggers and Greene[107]			
Purines											
Theobromine											
Theobromine sodium salicylate											
Theobromine sodium acetate								Wiggers and Greene[107]			
Theophyllin											
Theophyllin sodium acetate								Wiggers and Greene[107]			
Theophyllin ethylenediamine (E)	Fowler et al.[63] Mahaim and Rothberger[104] Laubry et al.[105]	Gold et al.[103]	Fowler et al.[63] Mahaim and Rothberger[104] Laubry et al.[105]			Wiggers and Greene[107]			Mahaim and Rothberger[104] Laubry et al.[105]	Gold et al.[103]	

A, In addition to the substances listed in the table, the following substances produced dilatation in heart-lung preparations or perfused heart preparations: Amphetamine sulfate (LeRoy),[65] camphor (Bodo)[60] (Kountz),[42] pilocarpine (Kountz),[42] morphine (Kountz),[42] papaverine (Kountz),[42] hypertonic sodium chloride (Katz et al.),[56] hypertonic calcium chloride (Katz et al.),[56] increased acidity of perfusion fluid (Smith et al.),[58] lack of oxygen (Richards),[109] increase in carbon-dioxide content (Anrep),[49] atropine (Hedbom),[75] diffusion substances liberated in myocardial ischemia (Katz et al.).[56]

The following substances produced constriction in the same type of preparation: Potassium chloride (Katz et al.),[56] atropine sulphate (Katz et al.),[56] (Kountz),[42] insulin (Bodo),[60] nicotine (Kountz),[42] (Krawkow),[66] barium chloride (Anitschkow),[74] (Krawkow),[47, 66] pilocarpine (Krawkow).[66]

In the intact unanesthetized animal the following substances produced an increase in coronary artery blood flow: Amphetamine sulphate (LeRoy),[65] papaverine (Essex et al.),[59] atropine sulphate (Essex et al.).[85]

In the intact anesthetized animals the following substances produced an increase in coronary artery blood flow, 1, 3-dimethyl-8-ethyl-xanthine (LeRoy and Speer),[110] and 1,3-diethyl-8-methyl-xanthine (LeRoy and Speer).[110]

*Studies of Kountz,[42] Kountz and Smith,[61] Anitschkow,[74] Krawkow[47, 66] were carried out on human hearts shortly after death. The studies by other investigators were carried out on laboratory animals.

B, In the studies of Wedd,[62] and Wedd and Fenn[51] adenosine, yeast, and muscle adenylic acid were used. The tissue extracts used by other investigators were of an unknown chemical nature.

C, Undilated human hearts were used in these studies.

D, Dilated human hearts were used in these studies.

E, In the experiments of Davis,[72] a constant head of pressure was employed to produce uniform distention of the coronary arteries. Any variation in the flow, therefore, was interpreted as due to changes in the coronary capillary blood flow.

F, In the studies of Voegtlin and Macht,[37] digitalein, digitalin, digitoxin, tincture of digitalis and bufagin caused coronary artery constriction. The water soluble digitonin and digalen produced dilatation. The infusion of digitalis caused constriction, followed by dilatation.

G, According to most investigators, the effect of histamine varies in different animal species. Thus in the intact cat, dog, and turtle, dilatation or an increased coronary blood flow is obtained, whereas, in the rabbit and guinea pig, constriction or a decreased coronary blood flow is induced.

treatment of cardiac pain." Massell,[12] using a similar technique for the relief of angina pectoris, found, however, that "the xanthines used, especially theocalcin, offer a better chance for the relief of angina pectoris in the ratio of 2 to 1 than aspirin, sodium bicarbonate, phenobarbital, or a combination of the latter two."

Objective Studies on Patients With Angina Pectoris.—Riseman and Brown,[13, 14] in a similar study, concluded: "it is obviously impossible to estimate how much of the apparent improvement was due to medication." They therefore measured the amount of work which patients could do following the administration of drugs and placebos. They found that "patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide, or tissue extract were unable to perform any more work than was possible without medication. . . ," whereas "one-half of the patients were benefited by using aminophyllin or quinidine sulfate." The value of nitroglycerin, erythrol tetranitrate, and atropine sulfate was demonstrated in a similar fashion. Wayne and Laplace,[15] using a similar method, obtained similar results with nitroglycerin, erythrol tetranitrate, and aminophyllin intravenously. Missal[16] and Kisch[17] also found that nitroglycerin and xanthine derivatives increased the exercise tolerance of patients with angina pectoris. Proger, Minnich, and Magendantz[18] found that "the abolition of cardiac irregularities by the use of quinidine sulfate resulted in a striking increase in the capacity for work without pain."

In 1932, Goldhammer and Scherf[19] showed that electrocardiograms taken during attacks of angina induced by deep knee bending revealed changes in the S-T segment and the T wave. These changes could be prevented and the amount of work performed could be increased by the administration of atropine sulfate before the onset of work. Larsen,[20] in 1938, found that the administration of nitroglycerin did not prevent the electrocardiographic changes which were induced by anoxia in patients with angina pectoris. Raab and Schönbrunner,[21] in 1939, found that the electrocardiograms of ten of fifteen patients with "an electrocardiogram of hypoxia" at rest or during exercise showed a tendency to become normal after roentgen irradiation of the adrenals. Levy, Bruenn, and Williams,[22, 23] in 1939, found that the administration of aminophyllin and nitroglycerin before breathing an atmosphere containing 10 per cent oxygen prolonged the time necessary to induce pain, and resulted in less change in the RS-T segments than was observed following lactose or no medication. When given intravenously, aminophyllin was more effective than nitroglycerin.

A survey of the literature on electrocardiographic changes during attacks of angina pectoris shows a marked difference of opinion as to the frequency and character of such changes.[24] This is probably due to differences in technique and different time relationships between the occurrence of pain and the recording of the electrocardiogram. Rise-

man, Waller, and Brown,[24] who took electrocardiograms *continuously* during exercise and during anoxia, have shown that the most constant change is a deviation (usually a depression) of the S-T segment in the precordial lead; this occurs before the onset of pain and disappears shortly after cessation of pain. Changes in the T wave were more common during recovery than during the attack. These investigators also found that the electrocardiographic changes induced by exertion could be prevented by the inhalation of pure oxygen before and during the exercise.

METHODS OF STUDY

Fifteen patients (fourteen men and one woman) with angina pectoris were studied. The youngest patient was 39 years of age; twelve were more than 50; the oldest was 56. The patients had been observed in a special clinic at weekly intervals for periods of one and one-half to seven years. At each visit the number of attacks experienced during the previous week was reported, and the amount of work necessary to induce pain was measured under standardized conditions.[25] All tests were carried out in a room maintained at a temperature of 45 to 55° F., approximately one hour after a light breakfast, and following at least one-half hour of rest after coming to the clinic; no tests were made if pain had been experienced on the way to the hospital; only one test was performed on any day. The exercise consisted of repeatedly mounting and descending a two-step staircase under the above conditions until the onset of pain.

On several visits electrodes were attached to both arms below the insertion of the deltoid muscles and also to the precordium over the cardiac apex. A precordial lead (IV R) was taken with the patient standing at rest; the exercise test was then repeated under the same standardized conditions, with the electrodes in place and the electrocardiographic machine (but not the camera) running continuously. Immediately before the cessation of exercise the camera was started, and a tracing was obtained for at least fifteen seconds after the onset of the attack; additional tracings were taken at one-minute intervals for five minutes after the cessation of pain.

After these studies were completed, drugs were administered in the usual therapeutic doses, and after an appropriate interval the exercise and electrocardiographic studies were repeated on at least two different days in an identical fashion.

The tests with nitroglycerin were carried out two minutes after the administration of a single dose (0.3 mg.). No other medication was administered for one week prior to these tests.

In the studies of theobromine sodium acetate, enteric-coated tablets (0.5 Gm.) were administered four times daily (on arising, after lunch, after supper, and before retiring) for one week; on arriving at the laboratory an additional dose (0.5 Gm.) of uncoated theobromine sodium acetate was administered. One to two hours later the electrocardiogram during exercise was obtained in the usual manner. Enteric-coated tablets of lactose, which were identical in appearance with the purine tablets, were used for control experiments; these were administered in the same manner and the tests carried out in an identical fashion.

The tests with quinidine sulfate were carried out after administering 0.3 Gm. of the drug four times daily for one week, with an additional dose one to two hours before the exercise and electrocardiographic tests. The inert substance used as a control for these studies was tablets of sodium bicarbonate (0.3 Gm.), which resembled the quinidine in appearance.

Studies on digitalis were performed in a somewhat different manner. Electrocardiograms were taken according to the technique described above, except that one precordial (IV R) and three standard leads were taken *continuously* before, during,

and after the exercise on four different days, during which period the patient received no medication. Tablets of digitalis leaf were then administered; 0.1 Gm. (1 cat unit) was given four times the first day and three times daily thereafter in an attempt to administer a full digitalizing dose according to the weight method of Eggleston.[26] All three patients, however, discontinued the medication, because of marked increase of pain, before receiving this calculated dose. The three patients weighed 140, 165, and 170 pounds, and received 1.4 Gm., 1.4 Gm., and 1.6 Gm., respectively, in a period of five days. Each patient returned to the clinic daily, at which time he reported the number of attacks he had experienced, and a four-lead electrocardiogram was obtained with the patient standing at rest. Exercise tests, using Lead IV R, were performed, in the manner described above, on two patients after the maximum degree of digitalization had been obtained, and, in the third subject, four days after digitalis was discontinued.

In the study of the electrocardiographic changes, ten consecutive complexes were measured and averaged. The terminal portion of the P-R interval was taken as the isoelectric level.

RESULTS

The amount of exercise necessary to produce pain was relatively constant (within six trips) for each of the fifteen patients. Immediately after the onset of pain caused by exercise, the electrocardiograms of all but one subject showed a depression of the S-T segment of 1 to 4 mm., as compared with the tracing taken at rest; the degree of depression was constant for each patient. The results after the administration of lactose or sodium bicarbonate were identical with those obtained when no medication was given. There was no correlation between the degree of depression of the S-T segment and the amount of work necessary to produce pain. Changes in the P, QRS, and T waves were inconstant and of little importance in these studies. There was nothing significant about the electrocardiogram during recovery from exercise and pain, except after the administration of digitalis.

The patients could be divided into three groups, according to their response to medication. The patients in Group I, after medication, showed little or no depression of the S-T segment as a result of exercise, and were able to do over 50 per cent more work than was possible when they were not taking drugs. Those in Group II, after medication, showed less depression of the S-T segment after exercise, and were able to do more work than was previously possible; these patients, however, showed some depression of the S-T segment after exercise, and developed pain when they performed 50 per cent more work than was possible when they were not taking drugs. The patients in Group III were not benefited by medication; after exercise they showed essentially the same changes in the S-T segment and were able to do no more work than was possible without medication. In general, when no medication was taken, the patients in Group I showed less depression of the S-T segment after exercise than did those in Group II or III.

Results With Nitroglycerin

The effect of nitroglycerin was studied on thirteen patients (Table II). Nine patients showed a marked response (Group I) (Fig. 1). In this

TABLE II

OBJECTIVE EVIDENCE OF THE EFFICACY OF NITROGLYCERIN IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION‡		2 MINUTES AFTER NITROGLYCERIN 1/200 GRAIN							
			NO INCREASE* IN WORK		50% INCREASE* IN WORK		100% INCREASE* IN WORK		MORE THAN 100%* INCREASE IN WORK	
	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)
Group I. S-T Changes Diminished Markedly Following Medication										
M. B.	36	3.0	36†	0.2						
S. E.	27	2.7	27†	0.2			54†	0.5	72	1.5
S. R.	51	2.7	51†	0.5	75†	1.0	100†	1.2	190†	1.5
H. Shl.	54	2.5	54†	0.4	75†	0.4				
B. L.	18	2.3	18†	0.5	26†	0.5				
M. L.	40	1.8	40†	0.0	64†	0.5				
H. Shr.	22	1.5	22†	0.0	36†	0.5	50†	0.3	100†	1.5
S. L.	26	1.5	26†	0.0	42†	0.2	60†	1.5		
R. C.	26	1.0	26†	0.0	39†	0.0				
Group II. S-T Changes Diminished Moderately Following Medication										
P. R.	49	3.5	49†	1.9	62	2.0				
L. W.	36	2.7	36†	2.5	61	1.0				
Group III. S-T Changes Not Prevented by Medication										
S. W.	38	1.6	38†	1.6	50†	1.6				
B. A.	50	4.0	50	3.0						

*Increase in work as compared with the amount necessary to induce pain when no medication was given.

†No attack of angina was induced.

‡Exercise was continued until attack was produced.

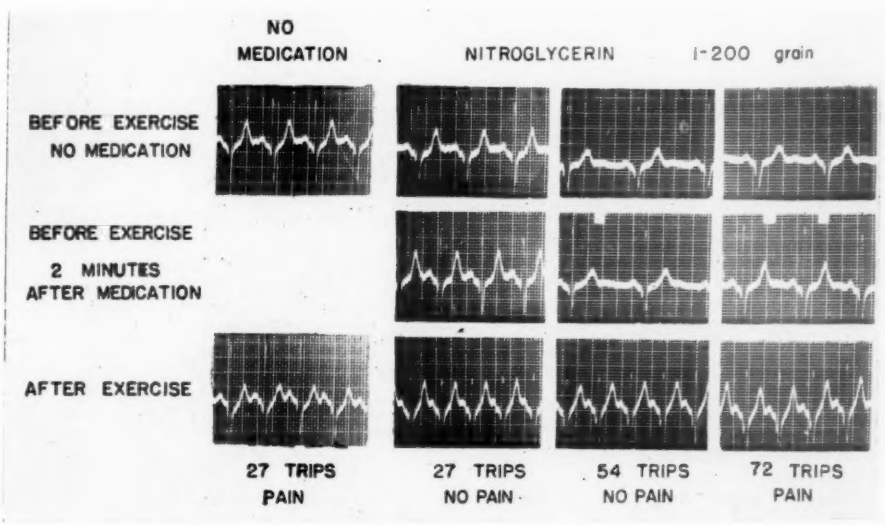

Fig. 1.—Marked response to nitroglycerin (Group I), as illustrated by results on Patient S. E. When no medication was administered, twenty-seven trips over the two-step staircase caused pain and a depression of the S-T segment averaging 2.7 mm. Two minutes after the sublingual administration of nitroglycerin, the same amount of work caused no pain and almost no change in the level of the initial portion (take-off) of the S-T segment; 100 per cent more work caused no pain and an average S-T depression of 0.5 mm; 150 per cent increase in work caused pain and an average S-T depression of 1.5 mm.

group the average depression of the S-T segment without medication was 2.1 mm. After the administration of nitroglycerin (0.3 mg.), the amount of work which previously induced pain caused an average depression of the S-T segment of only 0.2 mm., and no pain was experienced.

Two patients showed a moderate response to nitroglycerin (Group II). When no medication was taken, exercise sufficient to induce pain caused an average S-T depression of 3.1 mm. After medication, both patients performed 50 per cent more work before developing pain; the average depression of the S-T segment after this increased amount of work was 2.2 mm.

The remaining two patients showed no response (Group III); after exercise, approximately the same depression of the S-T segment occurred, both with and without medication. One was not benefited in any way by the drug (Fig. 2); the other was able to do more work than when nitroglycerin was not taken.

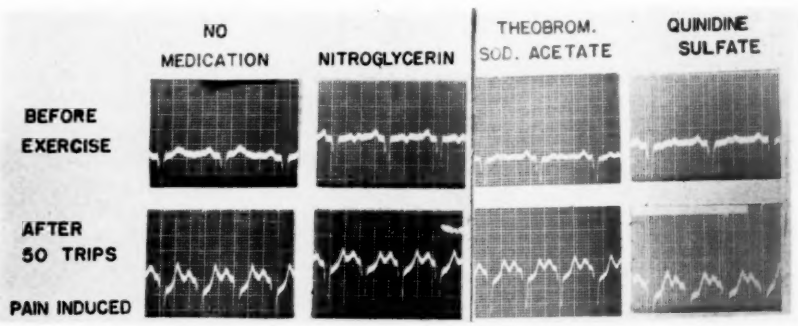

Fig. 2.—No response to medication (Group III), as illustrated by results on Patient B. A. When no medication was administered, fifty trips caused pain and an average depression of the initial portion of the S-T segment of 4.0 mm. The same results were obtained after the administration of nitroglycerin, theobromine sodium acetate, and quinidine sulfate.

Results With Theobromine Sodium Acetate

The effect of theobromine sodium acetate was studied on thirteen patients (Table III). Four showed a marked response to the drug (Group I). They were able to do at least 50 per cent more work before developing pain; the average depression of the S-T segment after exercise in these cases was 1.7 mm. before medication and 0.1 mm. after medication (Fig. 3).

Group II consisted of seven patients who did not develop angina on performing the same amount of exercise that produced pain when no medication was taken. The average S-T segment depression after exercise was 2.6 mm. when no drug was taken and 1.7 mm. after medication.

The remaining two patients (Group III) were unable to do more work after medication, and showed the same depression of the S-T segment that they had when no drug was taken (Fig. 2).

TABLE III

OBJECTIVE EVIDENCE OF THE EFFICACY OF THEOBROMINE SODIUM ACETATE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION‡		THEOBROMINE SODIUM ACETATE					
			NO INCREASE* IN WORK		50% INCREASE* IN WORK		100% INCREASE* IN WORK	
	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)
Group I. S-T Changes Diminished Markedly Following Medication								
S. R.	51	2.7	51†	0.2	66	3.5		
H. Shr.	22	1.5	26†	0.3	40†		50†	0.8
S. L.	26	1.5	26†	0.0			53	1.0
R. C.	26	1.0	26†	0.0	42†	1.0		
Group II. S-T Changes Diminished Moderately Following Medication								
M. B.	36	3.0	36†	2.4				
S. E.	27	2.7	27†	2.3				
H. Shl.	54	2.5	54†	1.6	74	2.8		
B. L.	18	2.3	18†	1.0				
M. L.	40	1.8	40†	0.7	54	1.0		
P. R.	49	3.5	49†	2.5				
L. W.	36	2.7	36†	1.5	55†	3.5		
Group III. S-T Changes Not Prevented by Medication								
S. W.	38	1.7	38†	1.7	50†	2.8		
B. A.	50	4.0	50	4.0				

*Increase in work as compared with the amount necessary to induce pain when no medication was given.

†No attack of angina was induced.

‡Exercise was continued until attack was produced.

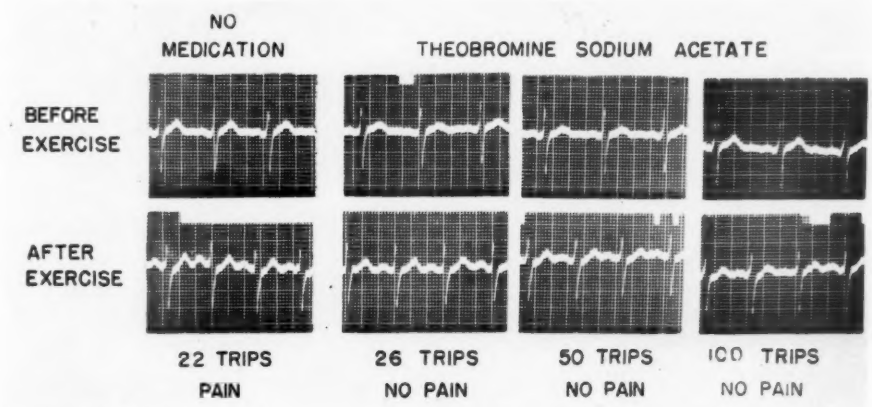

Fig. 3.—Marked response to theobromine sodium acetate (Group I), as illustrated by results on Patient H. Shr. When no medication was given, twenty-two to twenty-six trips produced angina and caused an average depression of the S-T segment of 1.5 mm. After medication, the same amount of work induced no pain and an S-T segment depression of 0.3 mm; after 100 per cent and 300 per cent more exercise no pain was induced and the S-T segment was depressed less than 1.0 mm.

TABLE IV

OBJECTIVE EVIDENCE OF THE EFFICACY OF QUINIDINE SULFATE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION**		QUINIDINE SULFATE					
			NO INCREASE§ IN WORK		50% INCREASE§ IN WORK		100% INCREASE§ IN WORK	
	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION (MM.)
Group I. S-T Changes Diminished Markedly Following Medication								
M. L.	40	1.8	40†	0.0	60	0.5		
H. Shr.	22	1.5	22†	0.0	*		40†	0.8
S. L.	26	1.5	26†	0.5	40*	1.2		
R. C.	26	1.0	26†	0.0	*		47	1.0
Group II. S-T Changes Diminished Moderately Following Medication								
M. B.	36	3.0	36†	1.6				
S. E.	27	2.7	27†	1.0	39†‡	1.5		
S. R.	51	2.7	51†	1.3	64†‡	1.5		
H. Shl.	54	2.5	54†	1.0	64†‡	1.3		
P. R.	49	3.5	47	2.0				
Group III. S-T Changes Not Prevented by Medication								
L. W.	36	2.7	36†	2.7				
S. W.	38	1.7	38†	2.3				
B. A.	50	4.0	50	3.5				

*No pain on performing 50 per cent more work than was possible when no medication was taken.

†No attack of angina induced.

‡No pain—patient stopped because of fatigue before performing 50 per cent more work than was possible when no medication was taken.

§Increase in work as compared with the amount necessary to induce pain when no medication was given.

**Exercise was continued until attack was produced.

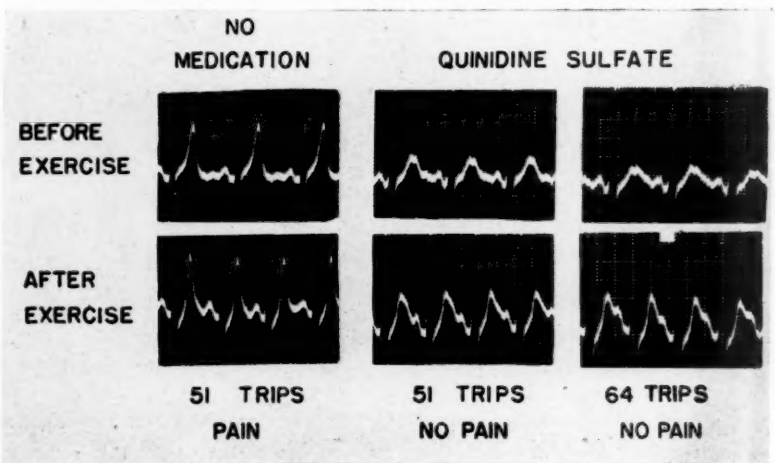

Fig. 4.—Moderate response to quinidine sulfate (Group II), as illustrated by results on Patient S. R. When no medication was administered, fifty-one trips over the two-step staircase induced an attack of angina and caused a depression of the S-T segment of 2.7 mm. After the administration of quinidine sulfate, an increased amount of work caused no pain and only 1.5 mm. depression of the S-T segment.

Results With Quinidine Sulfate

The effect of quinidine sulfate was studied on twelve patients (Table IV). Four showed a marked response, five, a moderate response, and three, no response. After exercise the average depression of the S-T segment of subjects in Group I was 1.5 mm. when no medication was taken, and 0.1 mm. after quinidine therapy. In Group II the average depression without medication was 2.9 mm., and, following medication, 1.4 mm. (Fig. 4). The average depression of the S-T segment of patients in Group III was 2.8 mm. when no medication was taken, and 2.8 mm. after the administration of the drug (Fig. 2).

After the administration of quinidine sulfate the electrocardiograms uniformly showed a prolongation of electrical systole (as measured from the beginning of the Q to the end of the T waves). This phenomenon has been recognized for some time.[27-29] The beneficial effects of quinidine were not dependent on this phenomenon, however, for prolongation of the Q-T interval occurred to the same degree in all patients (Figs. 2 and 4), irrespective of an increased ability to exercise after taking the drug.

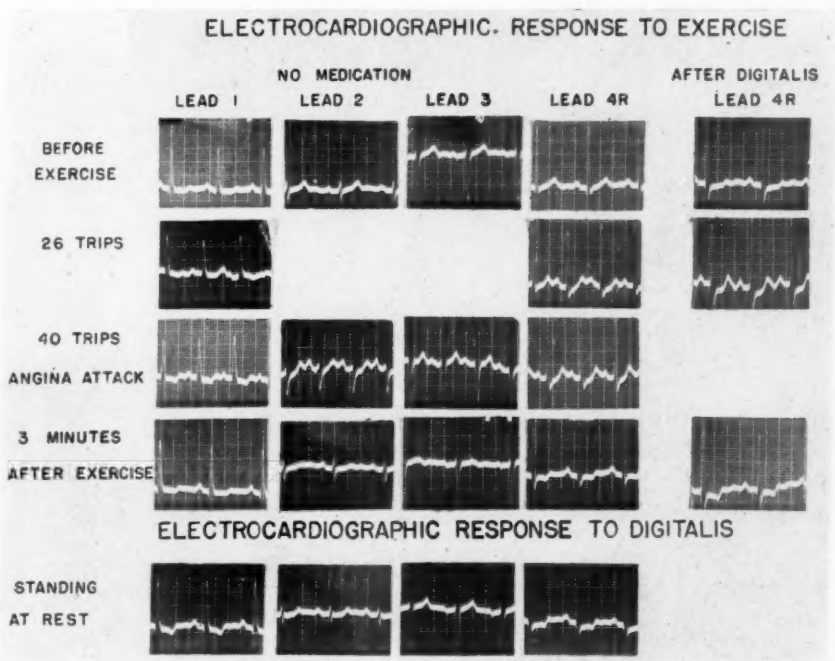

Fig. 5.—Patient M. L. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

Results With Digitalis

Studies on digitalis were discontinued because all three patients developed a marked increase in the frequency and the severity of their attacks of angina in daily life. After the administration of digitalis,

less work could be performed under standardized conditions before pain developed, and the electrocardiographic changes under such conditions were much more marked than those which occurred when no medication was given. Furthermore, following digitalis, the electrocardiogram with the patient standing at rest showed changes similar to those observed after exercise when no medication was given.

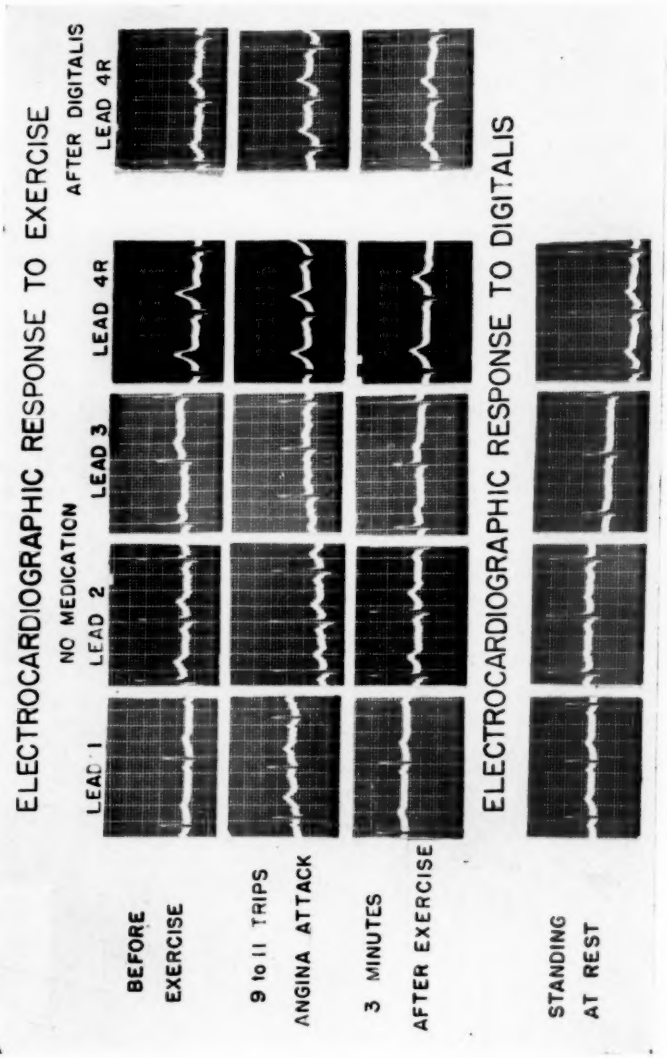

Fig. 6.—Patient N. B. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

Patient M. L. (Fig. 5) usually experienced one to two attacks each week, and his exercise tolerance was approximately forty trips. Beginning with the second day of digitalis therapy (after he had received 0.6 Gm.), he experienced several attacks of pain daily and complained of a constant sense of substernal pressure. He refused to con-

tinue digitalis therapy after taking 1.4 Gm. in five days, and, at that time, on performing twenty-six trips, he developed an attack more severe and about twice as long as usual. Before medication, exercise caused a definite depression of the S-T segment in Leads I, II, and IV, but Lead III showed few changes. After digitalis, Lead I, taken

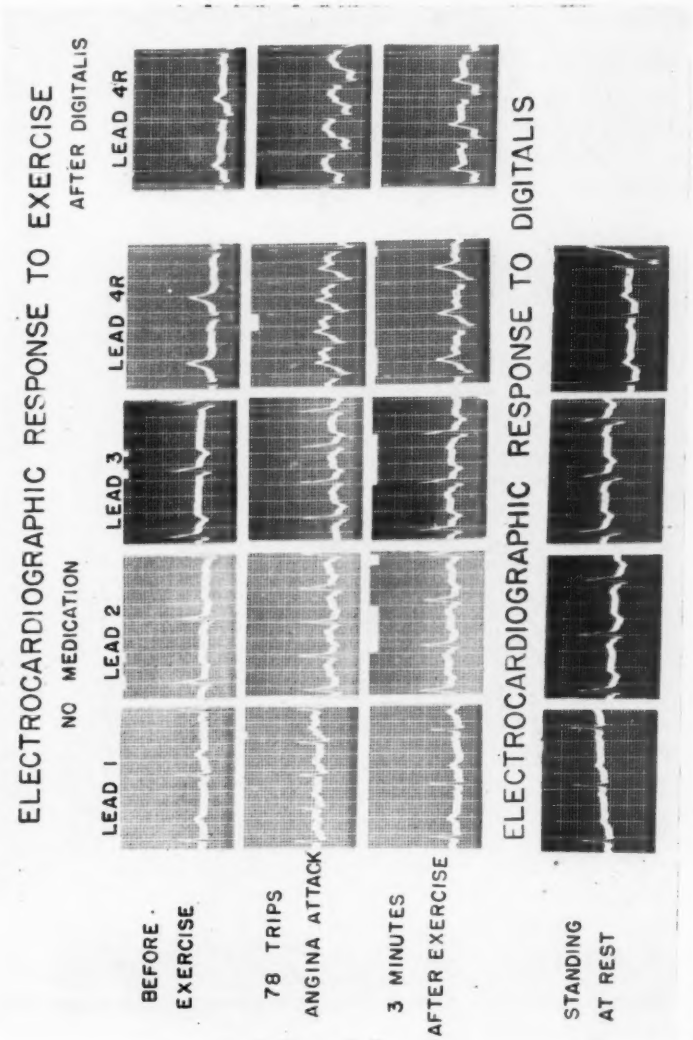

Fig. 7.—Patient H. B. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

with the patient standing at rest, was similar to Lead I immediately after the cessation of exercise when no medication was given; Lead IV was similar to that obtained three minutes after exercise; and Leads II and III showed no significant changes. After digitalis the electrocardiographic changes induced by twenty-six trips were greater than those observed after forty trips when no medication was given.

Patient N. B. (Fig. 6), during more than one and one-half years of observation, always developed an attack of one and one-half minutes' duration after eleven trips; he had been experiencing one to three attacks daily. After approximately one-half the digitalizing dose had been administered (0.6 Gm. in two days), he experienced an increase in pain during daily life. After receiving 1.4 Gm. of digitalis in five days the most severe attack that he had ever experienced (three and one-half minutes in duration) was induced by nine trips. The electrocardiographic changes during attacks induced by the small amount of work which could be performed without medication were minimal, and, therefore, the electrocardiographic response to vasodilating drugs was not studied. After the administration of digitalis the electrocardiogram (with the patient standing at rest) also showed minimal changes, except for a slight concavity in the S-T segment of Lead IV. Exercise after digitalis, however, produced marked changes, especially in the S-T segment of Lead IVR.

Patient H. B.'s reaction to vasodilating drugs was not studied because his attacks occurred rarely (less than once a week). Beginning with the third day of digitalis (1.0 Gm.) therapy, he experienced several attacks of pain daily. After exercise (Fig. 7), when no medication was given, Leads II and III showed little change, but in Leads I and IV there was a depression of the first portion of the S-T segment (1.5 and 2.8, respectively). After digitalis, with the patient standing at rest, similar though less striking changes were observed. Because of the marked increase in pain, exercise with electrocardiographic studies was not performed until four days after digitalis had been discontinued. At this time no pain was produced by the usual amount of exercise (seventy-eight trips); the test was stopped because of the marked electrocardiographic changes.

COMMENT

It is apparent from the above studies that the administration of nitroglycerin, theobromine sodium acetate, or quinidine sulfate enables some patients with angina pectoris to do a measurably greater amount of work under standardized conditions, and, at the same time, prevents the changes in the S-T segment which result from exercise; the administration of inert drugs has no such effect. The administration of digitalis to some patients with angina pectoris results in an increased frequency of attacks in daily life, a decrease in the amount of work which can be performed under standardized conditions, an increase in electrocardiographic changes following exertion, and changes in the electrocardiogram (taken with the patient standing at rest) similar to those observed after exercise without medication. These results show that the administration of nitroglycerin, theobromine sodium acetate, or quinidine sulfate in the dosage and manner customarily employed in the

treatment of such patients is of definite therapeutic value, whereas the administration of digitalis is harmful to some patients with angina pectoris.

These conclusions are in accord with the clinical experience of generations of physicians and patients, with the vast bulk of experimental evidence obtained on laboratory animals, and also with the objective electrocardiographic studies of Goldhammer and Scherf[19] and Levy, Bruenn, and Williams[22, 23] on patients with coronary artery disease, and with those of Zwillinger[30] on normal young subjects.

The present studies differ from previous investigations in that the conditions of the experiments resemble closely the clinical conditions under which attacks of angina pectoris occur in man; the drugs were administered to patients with angina in the customary therapeutic manner and dosage; the use of exercise to precipitate angina reproduces the conditions which induce attacks in daily life; and the electrocardiographic changes closely resemble those which occur consistently during attacks of angina pectoris.

The results and conclusions of the present investigation are not in accord with the careful clinical studies of Evans and Hoyle[8] and Gold, Kwit, and Otto.[11] The experiments of these investigators were controlled so carefully that the results cannot be dismissed unless adequate reason can be found for the discrepancy between their results and those of practically all other investigators. There is reason to believe that this discrepancy is due to the difficulties of evaluating the results of therapy in angina by purely clinical or subjective methods. In the last analysis, all such clinical evaluation depends on the ability of the patient and the investigator to differentiate between improvement resulting from medication and apparent improvement unrelated to therapy. It is not unusual for untreated patients to be free of pain for many days, and we have observed spontaneous remissions of a month or longer. Many factors, which are difficult to recognize, may cause this apparent improvement; these include a decrease in physical or emotional activity, a rise in the prevailing temperature, smaller and more digestible meals, and the beneficial psychologic effect of sympathetic medical supervision. Statistical clinical evaluation of the efficacy of treatment is further complicated by the fact that a large percentage (probably between 30 and 40 per cent) of patients with angina pectoris do not respond to any of the drugs in use today, and that the frequency of their attacks may vary spontaneously during investigation.

It was because of these difficulties that measurements of the patients' ability to exercise under standardized conditions were resorted to in these and previous studies.[13, 14, 24, 25, 31-34] The results of these measurements agree closely with the clinical response to therapy and are of considerable aid in differentiating between real and apparent improvement. Patients who are able to perform an appreciably greater amount

of exercise after medication usually experience a marked decrease in the frequency of attacks of pain in daily life; investigation of the daily routine of patients who show similar clinical improvement without an increased exercise tolerance usually reveals causes other than medication for the apparent improvement.

The methods used in this study are of considerable practical import. Many drugs have been placed on the market for the treatment of angina pectoris without adequate evidence of their efficacy. It is self-evident that the administration of inert or harmful drugs to patients with angina is dangerous and should be avoided by both the medical profession and the pharmaceutical houses. The simplicity of the methods used in this study, together with the direct clinical applicability of their results, suggests the advisability of requiring similar biologic assays of all drugs advocated for use in the treatment of angina pectoris.

The present and previous reports[13, 14, 24, 31, 34, 111] indicate that an evaluation of the efficacy of medication in the treatment of angina pectoris should include (1) *the incidence and degree of beneficial effects* (measured by the patient's ability to perform work under standardized conditions after administration of the drug in the dosage and manner usually employed in the treatment of angina pectoris), (2) *adequate control studies* (carried out in a fashion identical with the above, using both disguised medication and inert preparations of similar appearance), (3) *careful comparison of these results with the clinical response* (as estimated by the frequency of attacks in daily life while taking the drug, keeping in mind that apparent improvement may occur under medical supervision), (4) *objective electrocardiographic studies on patients, to confirm these results* (these objective studies should include the prevention of S-T segment changes associated with an increased ability to perform work in patients who are benefited by the drug, and the persistence of such S-T changes in patients who cannot increase their exercise tolerance after medication. Such objective electrocardiographic studies will reveal little if the action of the therapeutic agent depends on its analgesic properties, e.g., cobra venom or alcohol injection of the sensory pathways,[35] (5) *studies of the toxic effects of the drug* and a determination of the optimal dose, and (6) *comparison of the efficacy of the drug with that of other drugs* (especially nitroglycerin) which are commonly used in the treatment of angina pectoris.

An illustration of the practical use of this method in the evaluation of octyl nitrite is being reported.[31]

The results of the present investigation are in accord with the anoxemia theory of the production of angina attacks, and with the experimental evidence obtained on animals which indicates that the nitrites and purines are coronary vasodilators, whereas digitalis occasionally acts as a coronary vasoconstrictor. The deviation of the initial portion

of the S-T segment is apparently produced by myocardial anoxia, for it appears on breathing an atmosphere of low-oxygen content,[24, 36] and can be prevented by breathing pure oxygen before and during exercise.[24] Furthermore, these S-T changes are qualitatively, and frequently quantitatively, similar to those in clinical and experimental coronary arterial occlusion, when myocardial anoxia is known to exist. The prevention of the S-T changes during exercise suggests, therefore, that the drug has a vasodilating action on the coronary arteries, whereas the development or accentuation of changes may indicate a vasoconstricting action. Since patients with angina pectoris of arteriosclerotic origin suffer pain during exercise because of an inadequate flow of oxygenated arterial blood, rather than because of any unusual degree of arterial oxygen unsaturation, it is not surprising that the administration of the vasodilating drugs is more effective than breathing pure oxygen in preventing angina and the electrocardiographic changes induced by exercise.

SUMMARY AND CONCLUSIONS

When patients with angina pectoris exercise under standardized conditions, the amount of work which can be done before pain is induced is relatively constant for each person. Precordial lead electrocardiograms (IVR) taken before and *immediately after* exertion under these conditions show a change (usually a depression) in the level of the initial portion of the S-T segment, the magnitude of which is relatively constant for each subject.

When patients with angina pectoris are given nitroglycerin, theobromine sodium acetate, or quinidine sulfate, in the dosage and in the manner frequently employed in the treatment of this condition, many of the patients (more than one-half of the present series) are able to do more work under standardized conditions before pain is induced and show strikingly less change in the electrocardiogram. This increase in exercise tolerance is accompanied by a corresponding decrease in the frequency of attacks in daily life.

When the same patients are given lactose or sodium bicarbonate which has been disguised to resemble theobromine sodium acetate or quinidine sulfate, no increase in exercise tolerance occurs and the electrocardiographic changes are as great as when no medication is given. The clinical response to these inert drugs varies; apparent improvement may or may not occur, depending on conditions other than medication.

When patients with angina pectoris are given digitalis, an increase in the frequency and severity of cardiac pain sometimes occurs (in all three of the cases in the present series). This is accompanied by a decrease in the amount of work which can be done under standardized conditions, an increase in the electrocardiographic changes induced by work, and the development of changes in the electrocardiogram while

the patient stands at rest which resemble, in many respects, the electrocardiographic changes induced by exercise when no medication is taken.

The methods used in this study afford an objective means of testing the efficacy of drugs which are used in the treatment of angina pectoris under conditions closely comparable to actual clinical conditions. The results obtained by these methods yield objective evidence that nitroglycerin, theobromine sodium acetate, quinidine sulfate, and digitalis exert a specific effect on the heart.

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OCTYL NITRITE IN THE TREATMENT OF ANGINA PECTORIS

A. Stone Freedberg, M.D., Erwin D. Spiegl, M.D., and
Joseph E. F. Riseman, M.D.
Boston, Mass.

OCTYL nitrite (2-ethyl-n-hexyl-1-nitrite) is a liquid nitrite of one of the higher alcohols which, because of its volatility, can be administered by inhalation. Krantz, Carr, and Forman,[1] who first prepared this substance, state that in laboratory animals it produces a fall in systemic blood pressure and an increase in the coronary blood flow; it dilates isolated coronary artery rings, and, in normal men, the inhalation of large doses (0.2 c.c. for one minute) produces a moderate fall in blood pressure, together with a moderate increase in heart rate. As a result of their studies, the investigators concluded, "Employing cotton impregnated with octyl nitrite, the compound lends itself to medication in an inhaler in the treatment of angina pectoris, asthma, and paroxysmal hypertension."

Although this drug has been available commercially for over a year, no objective studies of its efficacy in the treatment of patients are on record. The purpose of the present communication is to present objective measurements of the advantages and disadvantages of the "octrite inhaler" in the treatment of patients with angina pectoris.

The methods used in this objective evaluation were presented in a previous communication,[2] and include (1) The incidence and degree of beneficial effects, as measured by an increased ability to perform work under standardized conditions after administration of the drug in the dosage and manner usually employed in the treatment of angina pectoris, (2) adequate control studies, carried out in an identical fashion with inert preparations, (3) comparison of these results with the clinical response when the drug is used in daily life, (4) electrocardiographic studies on the same patients to confirm the results obtained by the other methods, (5) studies of the toxic effects and optimal dosage, and (6) comparison of these results with those obtained with nitroglycerin.

MATERIALS AND METHODS

The inhaler tubes* used in this study were made of brown glass approximately 3 inches in length, closed at each end by screw caps. Each tube was filled with cellulose pellets which were impregnated with a total of 2 c.c. of octyl nitrite. The

From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University, Boston.
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directions on the tube and on the package read as follows: "Octrite should be administered only under careful supervision of a physician. Inhaler should be applied to one nostril, the other being closed, until relief begins, according to the physician's directions. Remove both caps during use."

The subjects used in this study were twenty patients (seventeen men and three women) with angina pectoris of arteriosclerotic origin. They were observed in a special clinic once each week for a period of at least six months. The response to medication was studied for at least two months. Each test was performed on at least two different occasions, but only one test was performed at any one visit.

The optimum dosage and the untoward effects of octyl nitrite were ascertained by having each subject inhale deeply one, two, or three times on separate days, and observing both the untoward and desirable effects. The character and severity of the untoward effects were ascertained by observation and by the patient's description of his reactions. The clinical efficacy was measured immediately after the inhalation in the manner described below.

The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion was studied in twenty patients by comparing the amount of work which could be performed after inhalation of the optimum dose of the drug with that which could be done both when no medication was administered and also after inhalation of ethyl acetate from a similar tube. The work, in each instance, was done under constant, standardized conditions[3] in a room kept at a temperature of 45 to 55° F., and consisted of repeatedly mounting and descending a two-step staircase until pain developed.

The efficacy of octyl nitrite was compared with that of nitroglycerin in nineteen of these patients. In these studies the amount of work which would be done after inhalation of octyl nitrite was compared with that which could be performed two minutes after placing a tablet of $\frac{1}{200}$ grain of nitroglycerin under the tongue.

Seventeen of these subjects were given octyl nitrite inhalers for home use. These patients were instructed to take the medication before any unusual physical or emotional strain. Once each week for eight to forty weeks these patients reported on the effect of the drug under these conditions.

The efficacy of octyl nitrite in shortening the duration of attacks of angina pectoris was ascertained in twenty patients by actual measurement in the laboratory, and also by clinical evaluation in eighteen of these subjects who tested the inhaler at home. In the laboratory the duration of attacks of angina pectoris induced by exertion was measured on several different days when no medication was taken. This was compared with the duration of attacks induced similarly on other days and treated immediately by the optimum number of inhalations of octyl nitrite. These results were also compared, in sixteen subjects, with the effect of placing nitroglycerin under the tongue immediately after inducing attacks by exertion.

After each of these tests in the laboratory, and also after each week of trial at home, the patient's evaluation of the efficacy of the drug in stopping attacks was recorded.

The duration of the effect of medication was studied by measuring on successive days the amount of work which could be performed at varying intervals after inhaling the optimum dose of the drug.

Electrocardiographic studies were carried out on nine patients according to a method previously described.[2, 4] On at least two different occasions, electrodes were attached to both arms below the insertion of the deltoid muscles, and also to the precordium over the cardiac apex. A precordial lead (IVR) was taken with the patient standing at rest; the exercise test was then repeated with the electrodes in place and the electrocardiographic machine (but not the camera) running continuously. Immediately before the cessation of exercise, the camera was started and

a tracing was obtained for at least fifteen seconds after the onset of the attack; additional tracings were taken at one-minute intervals for five minutes after the cessation of pain.

On two subsequent occasions, octyl nitrite (two inhalations) was administered two minutes before the onset of exercise. Electrocardiograms were taken as noted above. No other medication was administered during the week prior to these electrocardiographic studies.

In the study of the electrocardiographic changes, ten consecutive complexes were measured and averaged; the P-R interval was taken as the isoelectric level.

RESULTS

The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion (Fig. 1).—Inhalation of the drug enabled fifteen of the twenty patients to do an appreciably greater amount of work before developing angina. Six of these patients were able to do at least 50 per cent more work than was possible when they were not taking the drug, and four of these six were able to exercise to the point of fatigue without developing pain.

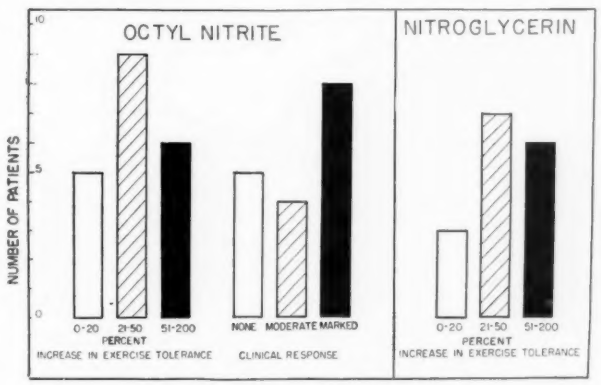

Fig. 1.—The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion, compared with the efficacy of nitroglycerin. The increase in exercise tolerance measures the frequency with which administration of drugs enabled patients to do more work under standardized conditions. The clinical response indicates the frequency with which the patients believed the drug to be of value when used in their daily life.

These results were similar to those obtained with nitroglycerin, except that the latter drug was somewhat more effective; it enabled six of nineteen patients to exercise to the point of fatigue without angina.

The five patients who were unable to do more work in the laboratory after taking the drug found the inhaler of no value in daily life. The remaining twelve of the seventeen patients who tested the drug at home reported that the inhaler was of definite value.

The efficacy of octyl nitrite in shortening the duration of attacks induced by exertion (Fig. 2) was best shown by the six patients whose attacks without medication were longer than one minute in duration.

Five of these patients showed a 17 to 64 per cent decrease in the duration of their attacks. These five patients also found that the drug was of value in shortening the duration of attacks experienced in daily life.

Only one of fourteen patients with attacks which were ordinarily less than forty-five seconds in duration showed an appreciable shortening of the attacks as a result of taking octyl nitrite. Another of this group showed an increase in the duration of pain following therapy. Similar results were obtained with nitroglycerin in eleven patients.

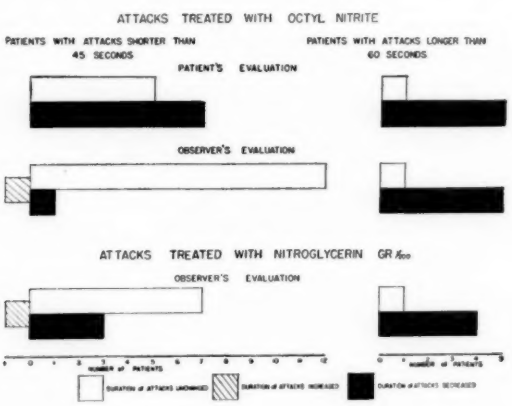
ATTACKS TREATED WITH OCTYL NITRITE
PATIENTS WITH ATTACKS SHORTER THAN 45 SECONDS
PATIENTS WITH ATTACKS LONGER THAN 60 SECONDS
PATIENT'S EVALUATION
OBSERVER'S EVALUATION
ATTACKS TREATED WITH NITROGLYCERIN GR 1/100
OBSERVER'S EVALUATION

Fig. 2.—The comparative efficacy of octyl nitrite and nitroglycerin in decreasing the duration of attacks of angina pectoris. The patient's evaluation indicates the frequency with which patients believed the drug to be of value when used in daily life. The observer's evaluation indicates the frequency of changes in the duration of attacks as ascertained by actual measurement.

Eight of twelve patients who tested octyl nitrite at home believe that the drug was of definite value in shortening the duration of the attacks. None of these patients believed that the medication prolonged the duration of pain.

The optimum dosage and untoward effects of octyl nitrite were ascertained by studying fourteen patients (Fig. 3). The amount of the drug which was absorbed could not be measured with any degree of certainty, for it varied with the depth of inspiration; accordingly, the comparative effects of one, two, and three *deep inhalations* were studied. The optimum dose differed somewhat in different patients. In general, inhaling more than once increased the frequency and the severity of untoward reactions without increasing significantly the amount of work which could be performed. The optimum dosage for most patients was, therefore, one deep inhalation, or less.

The untoward effects of octyl nitrite became evident approximately thirty seconds after the inhalation of the drug. First, there was a definite flushing of the face, and the patient experienced a sense of

warmth, together with a fullness and pounding in the head. After one to four minutes this pounding increased and was accompanied by severe headache and dizziness. After the larger doses the patient frequently became pale, perspired freely, and complained of weakness and faintness which were so severe in some instances that the patient was forced to lie down. This marked reaction never occurred after one inhalation; it was seen in only one instance after two inhalations and was observed in four cases after three inhalations. One other patient, not included

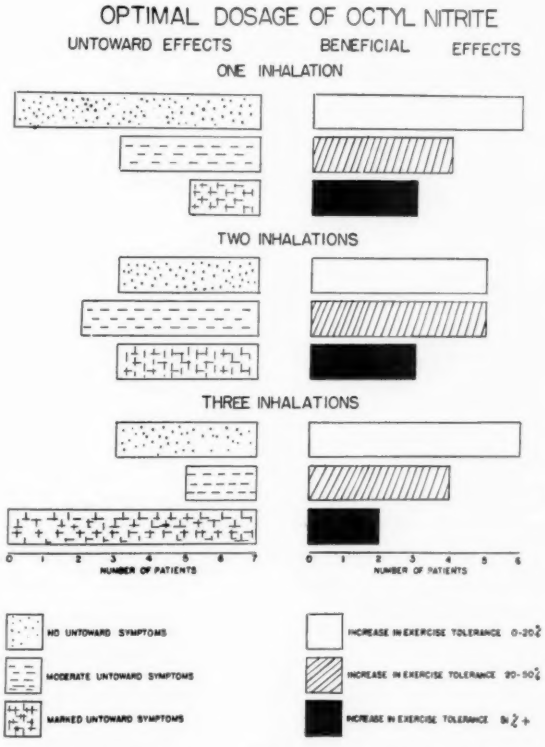

Fig. 3.—The optimal dosage of octyl nitrite.

in Fig. 3, took six inhalations in twenty-three seconds, was able to exercise for approximately one minute, and then collapsed. He complained of marked weakness, dizziness, and faintness. He appeared pale, perspired freely, and showed a marked fall in blood pressure, all of which persisted for approximately one-half hour. Three days later this patient was admitted to the hospital because of myocardial infarction, from which he recovered without complication. It is questionable whether this infarction was related in any way to the large dose of the drug which he absorbed; however, previous clinical reports[5, 6] have pointed out the harmful effects which may be induced by overdoses of nitroglycerin. Furthermore, Blumgart, Schlesinger, and Zoll[7]

have shown that shock, with its attendant fall in blood pressure, may cause fresh coronary occlusion.

The duration of action of octyl nitrite was measured on three patients (Fig. 4). One subject was enabled to perform more work for at least twenty minutes after one inhalation, and another had an increased exercise tolerance for eight minutes. The third patient received no benefit from the drug. It is evident, therefore, that the duration of the action of octyl nitrite (like that of nitroglycerin) differs in different patients.

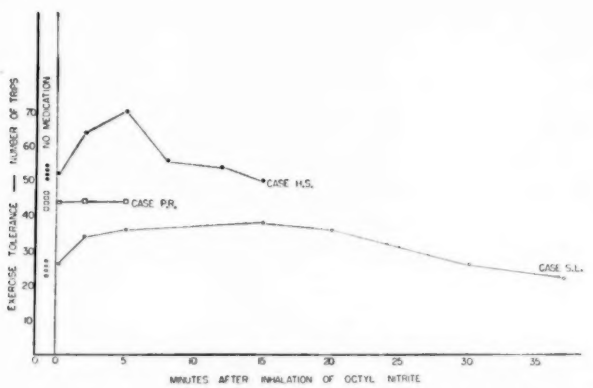

Fig. 4.—The duration of action of octyl nitrite.

TABLE I

OBJECTIVE EVIDENCE OF THE EFFICACY OF OCTYL NITRITE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION**		OCTYL NITRITE			
			NO INCREASE IN WORK§		50% INCREASE IN WORK§	
	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)
Group I. S-T Changes Markedly Diminished Following Medication						
H. Shl.	54	2.5	54†	0.5	81†	1.5
M. L.	40	1.8	40†	0.5	62‡	0.5
H. Shr.	22	1.5	22†	0.0	40†	
S. L.	26	1.5	26†	0.2	42†	
R. C.	26	1.0	26†	0.0	42†	
Group II. S-T Changes Moderately Diminished Following Medication						
S. E.	27	2.7	27†	2.0		
L. W.	36	2.7	36†	1.8	54	1.4
Group III. No S-T Changes Following Medication						
P. R.	49	3.5	47	3.1		
B. A.	50	4.0	50	4.0		

*The average of the measurement of ten consecutive complexes.

†No attack of angina induced.

‡No pain on performing 50 per cent more work than was possible when no medication was taken.

§Increase in work as compared with the amount necessary to induce pain when no medication was given.

**Exercise was continued until attack was produced.

Electrocardiographic studies were made on nine patients (Table I). When no medication was given, the electrocardiograms immediately after the onset of pain induced by exercise showed a depression of the S-T

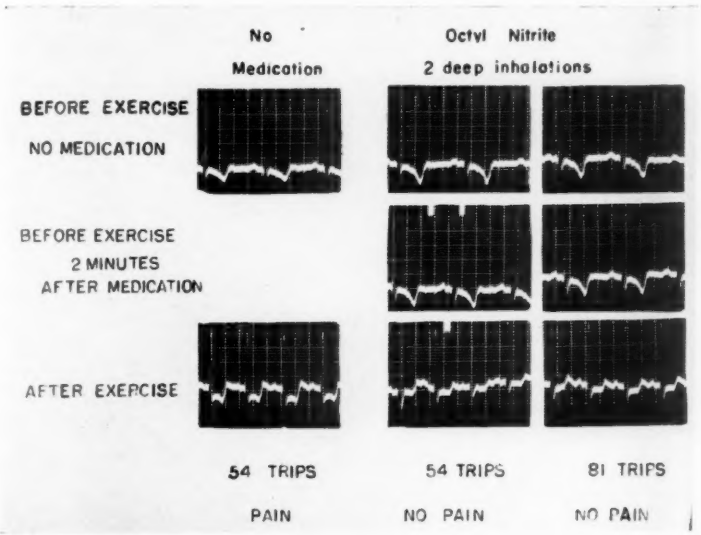

Fig. 5.—Marked response to octyl nitrite (Group I), as illustrated by results on patient H. Shl. When no medication was administered, fifty-four trips over the two-step staircase caused pain and a depression of the S-T segment averaging 2.5 mm. Two minutes after two inhalations of octyl nitrite the same amount of work caused no pain and a depression of the S-T segment of but 0.5 mm.; 50 per cent more work resulted in no pain and an average S-T segment depression of 1.5 mm.

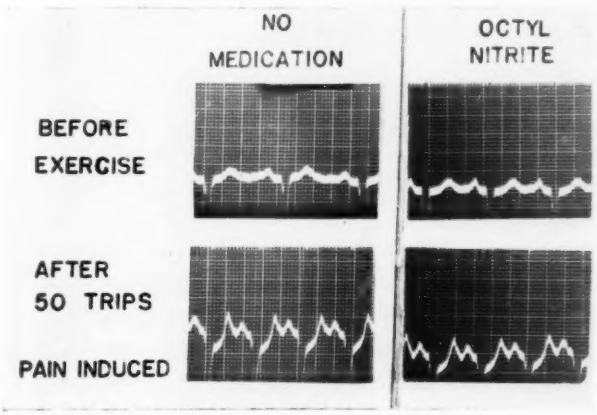

Fig. 6.—No response to octyl nitrite (Group III), as illustrated by results on patient B. A. When no medication was administered, fifty trips over the two-step staircase caused pain and an average depression of the initial portion of the S-T segment of 4.0 mm. The same results were obtained after inhalation of octyl nitrite.

segment of 1 to 4 mm., as compared to tracings taking at rest. This change was constant for each subject. Changes in the P, QRS, and T waves were variable and inconstant.

The inhalation of octyl nitrite with the patient standing at rest resulted in an average increase in heart rate of 11.6 beats per minute. Inhalation of the drug caused no constant change in the P, QRS, or T waves.

Five patients showed a marked change in the S-T segment as a response to the drug (Fig. 5). After exercise, the average depression of the S-T segment, when no medication was taken, was 1.7 mm., whereas, after medication, it was 0.2 mm. All five patients were able to do at least 50 per cent more work without developing pain. Two patients showed a moderate response to the drug; the average depression of the S-T segment after exercise when no medication was taken was 2.7 mm., and following the same stimulus after octyl nitrite was 1.9 mm. The remaining two patients showed no response to medication, either in an increased ability to work or in prevention of the S-T segment changes following exertion (Fig. 6).

The duration of efficacy and cost of the inhaler tube.—Four patients used the inhaler tube at home until it was no longer of any value in preventing or shortening the duration of attacks. The number of treatments before the tube became depleted was 44, 75, 120, and 180, respectively. Therefore, the cost of the medication was one to four cents per dose, or two to eight times that of nitroglycerin.

Observations on inhalation as a method of administering nitrites.—Although inhalation medication would seem to be a simple procedure, it was found that patients could not follow the directions on the label of the inhaler tube, and they obtained no benefit from the drug until the method of administration was demonstrated by the physician on at least one and frequently two or three different occasions.

Many difficulties were experienced with the commercial, glass inhaler tube. Breakage of the inhaler (which happened to at least one-third of the tubes which were used at home) was caused not only by dropping, but also by removal of the caps. The frequency of breakage not only added appreciably to the cost, but also deprived the patients of medication temporarily. The method of retaining the pledgets within the tube was faulty, for they would frequently fly into the nostril on deep inhalation. A further objection to the inhaler was the necessity for removing the two caps closing the ends; this frequently resulted in fumbling and loss of valuable seconds before the patient was able to take the medication. Although the patients found the odor of the drug unpleasant, it was not so objectionable as to prevent continuation of its use.

COMMENT

It is evident that octyl nitrite is definitely effective in the treatment of angina pectoris. This was shown objectively, not only by an increased ability to work after inhalation of the drug, but also by a definite decrease in the duration of the attacks in some cases. Further-

more, this drug, like others which are effective in angina pectoris,[2] prevents the development of the electrocardiographic changes which ordinarily occur on exertion in patients with angina.

Octyl nitrite is apparently similar in its action to nitroglycerin and amyl nitrite, and it has all of their advantages and disadvantages. It differs from nitroglycerin primarily in that, being volatile, it can be administered by inhalation; this attribute permits wide variation of the dosage but appears to be of little practical value. It is superior to nitroglycerin in that it is absorbed rapidly. This should make it more suitable than nitroglycerin for shortening the duration of attacks. In our experience, a rapidly soluble tablet of nitroglycerin requires twenty seconds for solution, and the effect of the drug becomes evident approximately one minute after placing it under the tongue.[3] Octyl nitrite requires ten seconds, or less, for one inhalation, and the effect becomes evident within thirty seconds. Since attacks of angina pectoris are usually less than three minutes in duration,[3] any method of treatment which makes the drug available more rapidly is of value. Octyl nitrite is more expensive than nitroglycerin, but less costly than amyl nitrite ampules. This is its main advantage over the latter drug.

These are definite drawbacks to the inhaler tube now on the market. The method of packaging makes it obvious that it is meant primarily for sale across the counter, and not solely on prescription. If the directions on the package are followed and the patient continues inhaling until relief begins, severe and even dangerous reactions may occur. One inhalation, only, should be used unless careful observation by the physician or the patient indicates that larger doses are safe and necessary. It is evident that the patient must be taught to use the inhaler correctly. It would seem advisable to modify the tube, not only to prevent breakage, but also to improve it mechanically so that the drug would be available more rapidly without the necessity of fumbling with the caps.

CONCLUSIONS

Octyl nitrite can be administered to patients with angina pectoris by the inhalation method. It is an effective means of preventing attacks on exertion and cutting short the duration of such attacks. Its action is similar to that of nitroglycerin and amyl nitrite, in both its beneficial and its untoward effects. It differs from nitroglycerin primarily in the mode of administration, which permits more rapid absorption but makes accurate dosage impossible. The commercial inhalers now available are not satisfactory. Dose for dose, octyl nitrite is much more costly than nitroglycerin, but less so than amyl nitrite.

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THE EFFECT OF ABRASION OF THE SURFACE OF THE HEART UPON INTERCORONARY COMMUNICATIONS

EUGENE J. STANTON, M.D., PAUL SCHILDT, M.D., AND
CLAUDE S. BECK, M.D.
CLEVELAND, OHIO

EXPERIMENTS are recorded in which the surface of the heart was abraded by means of a metal burr, and the effect of this procedure upon the coronary arterial circulation was determined.

Abrasion of the surface of the heart was a component of the operation introduced by Beck[1] in the treatment of coronary artery sclerosis. The other components of this operation were the use of a foreign body, such as powdered beef bone, on the surface of the heart, and the grafting of vascularized tissues, such as fat, parietal pericardium, and skeletal muscle, upon the surface of the heart. The purpose of abrading the surface of the heart in this operation was to remove the epicardial barrier between the coronary arteries and the arteries of the grafted tissues. The purpose of using powdered beef bone was for the production of an inflammatory (foreign body) reaction on the surface of the heart. It was also pointed out in this paper that distribution of blood to every part of the myocardium was of vital importance. It was demonstrated experimentally that a small area of the heart muscle which had been made ischemic by the ligation of several peripheral branches of the coronary arteries became a trigger zone that set off ventricular fibrillation, whereas a much more marked reduction of total coronary flow was tolerated when the occlusion was placed centrally at the origin of the coronary arteries. It was also shown experimentally that complete occlusion of a major coronary artery was tolerated better if a vascular bed had been prepared by a previous operation. Ligation of the right coronary artery was followed by a recovery rate of 30 per cent in the normal heart and 66 per cent in the prepared heart.[2] This operation protected the heart in two ways: (1) It provided an extracoronary source of blood supply, and (2) it produced a more equitable distribution of blood between coronary arteries. Both extracoronary and intercoronary communications were demonstrated as a result of applying surgical procedures to the heart.[3] "It seems quite possible," according to Mautz and Beck, "that the epicardial injury produced at the time

From the Laboratory of Surgical Research, Western Reserve University School of Medicine, and University Hospitals of Cleveland.
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of operation may lead to new intercoronary communications, when the injury is produced at the junction between obstructed and nonobstructed coronary arteries. As granulation tissue proliferates to repair an injury, new arterioles develop and in this way new arterial communications may form between two coronary arteries.'' Intercoronary communications which were produced by surgical methods were illustrated in Fig. 8 of that publication. However, studies have not been made to ascertain the relative importance of these factors. The experiments reported here concern intercoronary communications without the presence of extracoronary communications. This publication deals with the effect of abrading or scraping off the epicardium. A later publication will concern the effect of powdered beef bone and other agents upon the development of intercoronary communications.

EXPERIMENTS

A. The Coronary Arteries in the Normal Heart and in the Abraded Heart

In ten experiments on dogs the entire surface of the heart was thoroughly abraded. Frequently the epicardium came away in sheets of 1 sq. cm. or larger. The experiment was terminated one week to three months later. The circumflex ramus of the left coronary artery and the right coronary artery were cannulated, washed with a little physiologic saline, and injected with a barium sulfate gelatin mixture under a pressure of 200 mm. of mercury.[4] This injection mass entered small arterioles, but did not fill capillaries and arterioluminal vessels. These two arteries in normal hearts were similarly injected for comparison. Roentgenograms of the specimens were taken (Figs. 1 and 2). The amount of injection mass that passed over into the descending ramus of the left coronary artery was variable in each individual heart. The amount that did pass over was assumed to be an indication of the size and number of intercoronary communications between the beds that were cannulated (circumflex ramus of left coronary artery and right coronary artery) and the noncannulated bed (descending ramus of left coronary artery). Analysis of these results is shown in Fig. 3. According to this comparative classification, a good injection was obtained in five abraded hearts and in no normal heart; an intermediate injection was obtained in two normal hearts and in one abraded heart; a slight injection was observed in four normal hearts and in one abraded heart; and no injection occurred in four normal hearts and in three abraded hearts. It should be pointed out that a considerable variation existed in the communications between one coronary artery and another. A rare specimen was found among normal hearts in which these communications were numerous and large enough to transmit blood, whereas other specimens failed to show any communications.[3] It is obvious from this study that the abraded hearts as a group are different from the normal

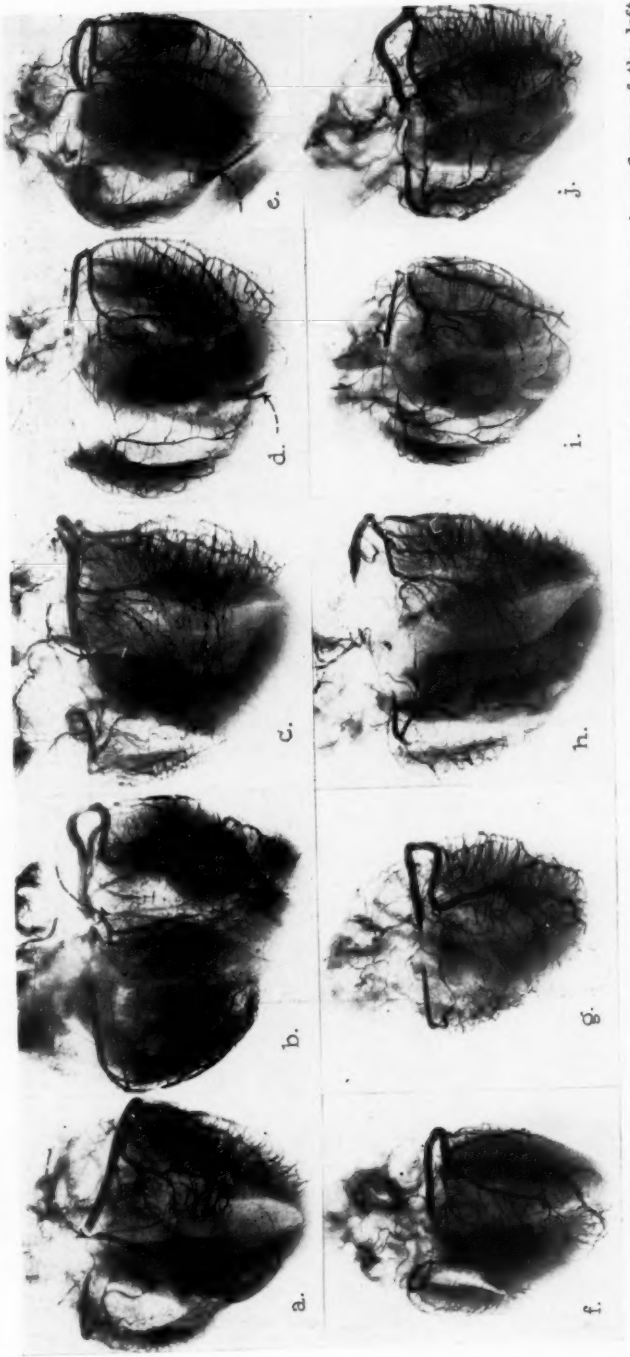

Fig. 1.—Roentgenograms of the normal hearts with barium sulfate gelatin mixture injected into the ramus circumflexus of the left coronary artery and the right coronary artery. Note the injection of the descending ramus of the left coronary artery in *a*, *b*, *c*, *d*, and *e*, as indicated by arrows, and the absence of injection of this artery in the other specimens.

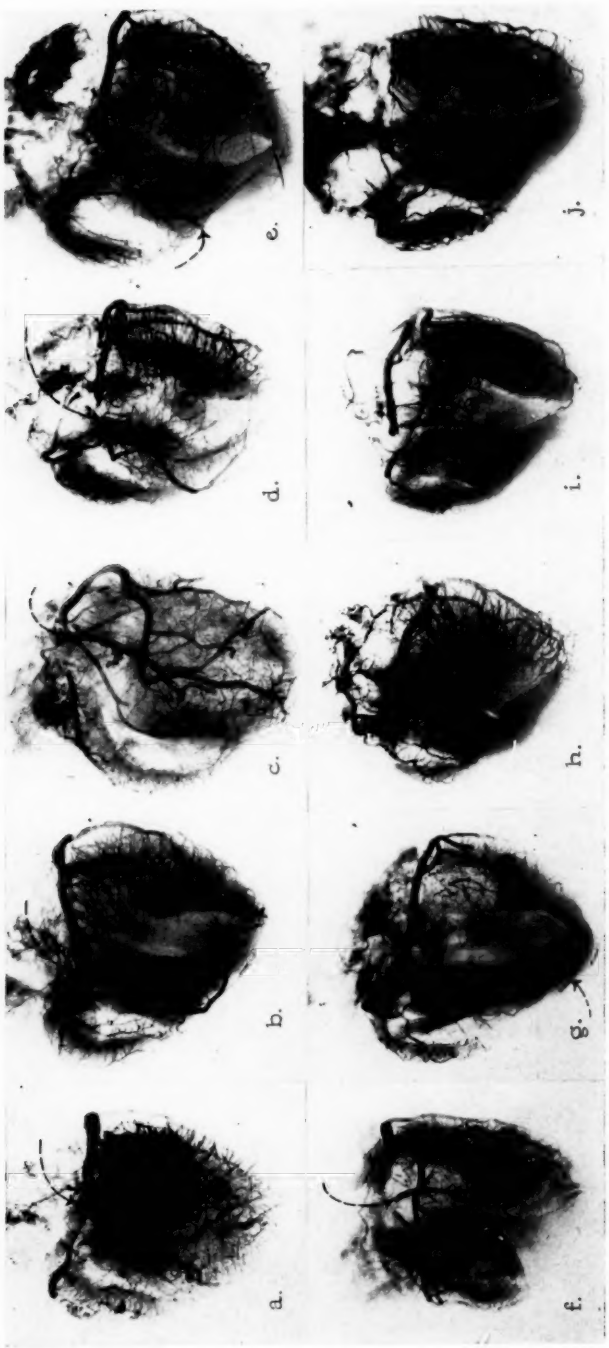

Fig. 2.—Roentgenograms of ten hearts, the surfaces of which were abraded one week to three months before injection. Specimens were injected as in Fig. 1. Note the injection of the descending ramus of the left coronary artery in *a*, *b*, *c*, *d*, *e*, *f*, and *g*, as indicated by arrows, and the absence of injection of this artery in the other specimens.

hearts as a group. The difference between the two groups is better injection of the descending ramus in the abraded specimens. Indeed, it seems that one might be able to select the hearts that might survive ligation of the descending ramus of the left coronary artery at its origin in one step and those that might not survive ligation of this artery. We should expect survival to take place in *a*, *b*, *c*, *d*, *e*, and *f* of the abraded group (Fig. 2), and in *a*, *b*, and questionably in *c* of the nonabraded group (Fig. 1). This estimate can be compared with results obtained in 110 experiments in which this artery was ligated.

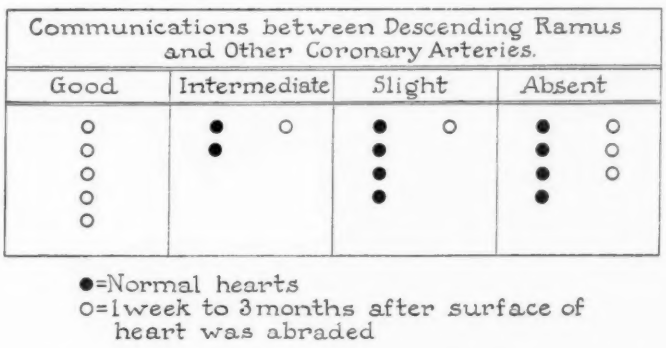

Fig. 3.—Ten normal and ten abraded hearts injected with barium sulfate gelatin into circumflex branch of left coronary artery and into right coronary artery. The specimens are classified according to the amount of the injection mass found in the descending ramus of the left coronary artery.

B. Ligation of the Descending Ramus of the Left Coronary Artery at Its Origin in Normal Hearts and in Abraded Hearts

Mortality.—Ether anesthesia was used. Artificial respiration was carried out by means of an intratracheal tube. A surgical dissection of the descending ramus of the left coronary artery at its origin was made. The common left artery was exposed at its bifurcation. Two ligatures were placed on the descending ramus, and the artery was transected between ligatures. In this way only can we be certain that ligation of the artery is proximal to its highest branches. Ligation at lower levels has introduced a variable factor that is not uncommonly referred to in the literature. This artery was ligated in five groups of ten dogs each. In one group two operations were performed because it was suggested that two exposures of the heart might make some difference in the result. In this group the dissection of the artery was carried out, and a piece of silk was passed beneath the vessel; no obstruction to the vessel was produced. Two weeks later the artery was doubly ligated and transected. The result was that four dogs lived and six died. The total mortality is shown in Table I. Recovery occurred in fifteen experiments, or 30 per cent, and death occurred in thirty-five experiments, or 70 per cent. The variations in the five groups of ten each ranged from

recovery of one to recovery of five. We feel that this difference must be due to variations in individual hearts with regard to the number and size of intercoronary communications and the relative size and importance of the three major arteries themselves.

TABLE I A

LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

DOGS	LIVING	DEAD
10	3	7
10	1	9
10	4	6
10	2	8
10	5	5
Total 50	15 (30%)	35 (70%)

TABLE I B

ABRASION OF EPICARDIUM FOLLOWED BY LIGATION OF ARTERY

DOGS	INTERVAL (WEEK)	LIVING	DEAD
10	Same operation	4	6
10	1	6 (60%)	4
20	2	14 (70%)	6
20	3	11 (55%)	9
Total 50		31 (62%)	19 (38%)

Results of 110 experiments, in fifty of which the descending ramus of the left coronary was ligated and cut at its origin, and in sixty of which the surface of the heart was abraded before ligation and section of the same artery.

In ten experiments the surface of the heart was abraded, and after this was done, and at the same operation, the descending ramus of the left coronary artery at its origin was doubly ligated and transected as in the control experiments. The result in this group was that four lived and six died. This result was the same as that in one of the control groups, and indicates that no obvious benefit was obtained by abrasion when the two procedures were done simultaneously.

In one group of ten and two groups of twenty experiments each, abrasion of the heart was followed by ligation and section of the artery, as in the control groups, at intervals of one, two, and three weeks, respectively, between abrasion and ligation. The results of these experiments, in order, were that six lived and four died; fourteen lived and six died; and eleven lived and nine died. The total result was thirty-one survivals, or 62 per cent, and nineteen fatalities, or 38 per cent (Table I). All animals were kept for periods of at least two months after ligation of the artery in order to obtain these statistics. According to these results, the mortality after ligation of the descending ramus of the left coronary artery at its origin, in one step, was reduced from 70 per cent in fifty normal hearts to 38 per cent in fifty hearts in which the surface of the heart had been abraded one to three weeks before the artery was ligated.

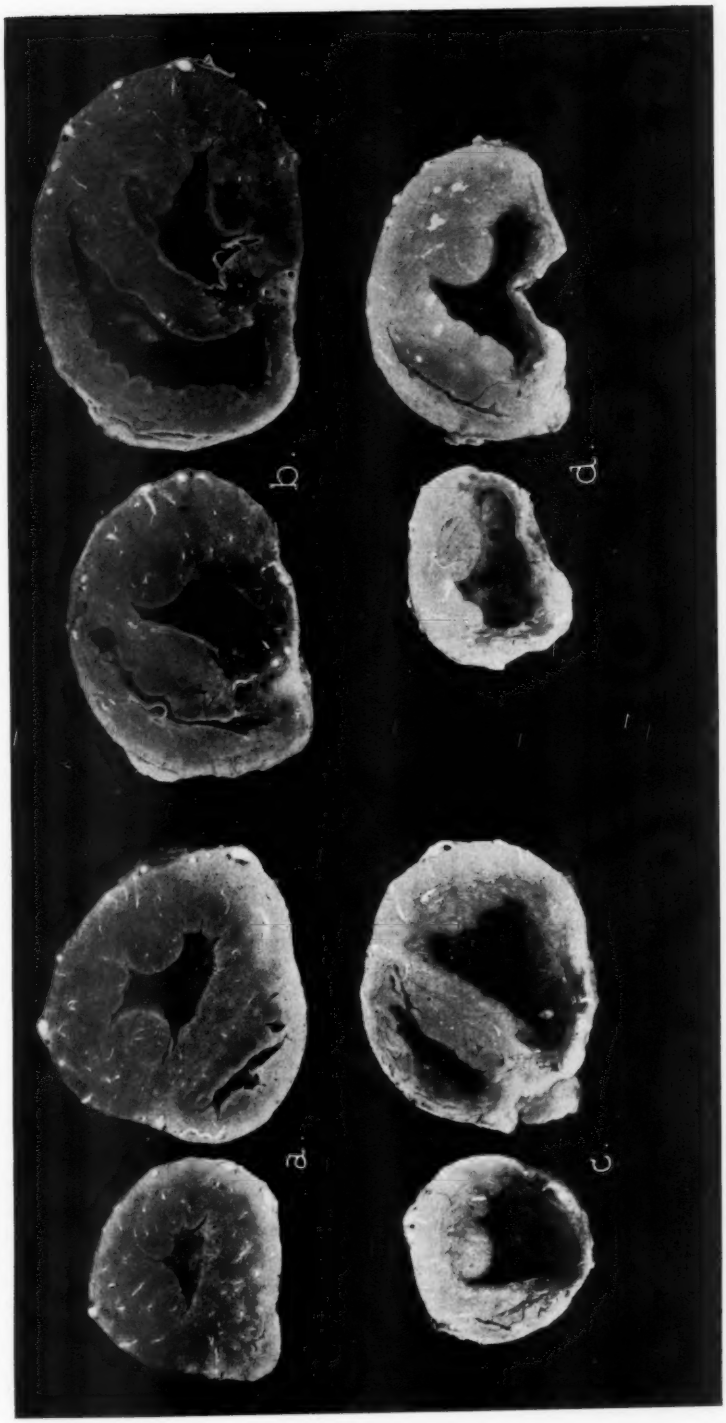

Fig. 4.—The specimens were arranged into four groups according to the size of the infarct. *a*, No infarct; *b*, small infarct; *c*, intermediate infarct; and *d*, large infarct. This is key for Fig. 5.

Infarcts.—At any time after a two-month period the experiment was terminated and the specimen examined. The circumflex branch of the left coronary artery and the right coronary artery were cannulated and injected as in the control groups. The descending ramus of the left coronary artery was not injected. The specimens were chilled after injection to fix the injection mass, and the specimen was preserved in formalin. After fixation, roentgenograms of the specimens were taken and then four or five transverse sections were made across the heart. The infarcts were classified, according to size, as none, small, intermediate, and large. Examples from this classification are shown in Fig. 4. With this illustration as a key, the specimens were arranged in groups, as shown in Fig. 5. In two specimens no infarct was found. Both of these hearts had been abraded before the artery was ligated. A small infarct was found in four control specimens and in seven abraded specimens. An intermediate infarct was found in four control specimens and in ten abraded specimens. A large infarct was found in seven control specimens and in twelve abraded specimens.

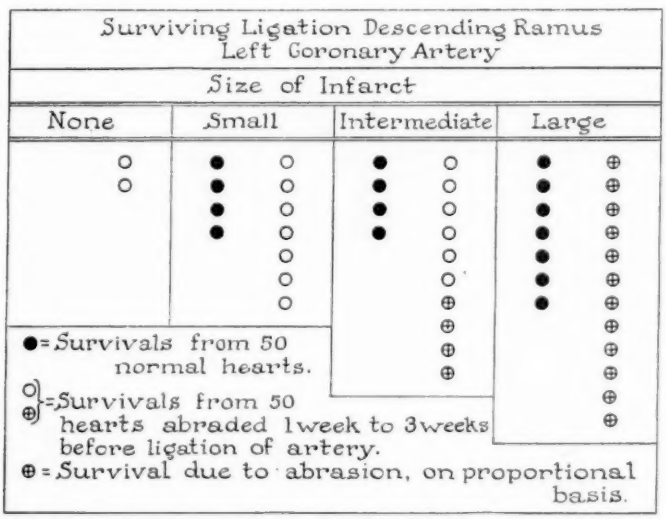
Surviving Ligation Descending Ramus Left Coronary Artery
Size of Infarct
None
Small
Intermediate
Large
●=Survivals from 50 normal hearts.
○ ⊕ =Survivals from 50 hearts abraded 1 week to 3 weeks before ligation of artery.
⊕=Survival due to abrasion, on proportional basis.

Fig. 5.—Results with fifty abraded and fifty normal hearts in which the descending ramus of the left coronary artery was ligated in one step at its origin. The group in which abrasion and ligation were done at the same operation is not included.

Two conclusions are obvious in the analysis of these results. One is that abrasion tends to reduce the size of the infarct, making it possible to ligate the descending ramus of the left coronary artery at its origin without the formation of an infarct. This, in our experience, never occurred in a normal, unabraded heart. The other conclusion is that there are more abraded specimens than control specimens in every group—small, intermediate, and large. On a percentage basis, it appears that the lives of sixteen of fifty dogs were saved by abrasion of the surface of the heart before the artery was ligated.

Injected Specimens.—On examination of the specimens it was found that many of the hearts that survived ligation of this artery, whether of the control group or of the abraded group, showed well-developed communications between the ligated artery and the other two patent arteries (Fig. 6). Good communications were present regardless of the size of the infarct. It would appear from these results that, if recovery followed ligation of the descending ramus of the left coronary artery, the entire vascular bed frequently became one common bed. The cause for the development of a common arterial bed is the existence of a pressure differential in the open arterial tree, as compared to the closed

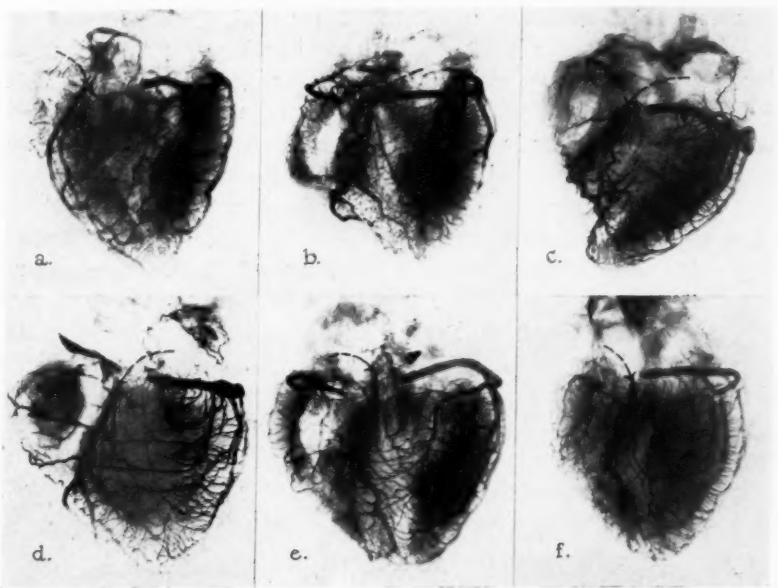

Fig. 6.—Roentgenograms of hearts that survived ligation of the descending ramus of the left coronary artery at its origin. The right coronary artery and the circumflex branch of the left coronary artery were injected. The descending ramus filled well through intercoronary communications, which became progressively larger after ligation, regardless of the size of the infarct. A common coronary bed was produced by the ligation; this is a favorable condition in the presence of progressive coronary artery sclerosis. Arrow points to the ligated descending ramus.

arterial tree. It is conceivable that the small anatomic communications that normally extend into adjacent vascular beds are opened up by this pressure gradient.[5] These communications undergo progressive enlargement until they carry a considerable quantity of blood. This is a favorable anatomic and physiologic condition, and it should offer a degree of protection against further coronary occlusion. In a study of human hearts with coronary artery disease, Blumgart, Schlesinger, and Zoll[6] found that, in the majority, two of the three major arteries were occluded. After the subject survived occlusion of one major artery and after a common coronary bed developed, it would appear that this com-

mon circulatory tree was adequate to carry on until another major artery was occluded. Were it not for the development of a common bed, one would expect catastrophe earlier in the course of the occlusive process.

SUMMARY AND CONCLUSIONS

We have demonstrated that intercoronary communications can be produced by surgical methods. Abrasion of the surface of the heart was the surgical method used in these experiments. This surgical procedure was effective in opening intercoronary communications. It reduced the death rate from 70 per cent to 38 per cent after ligation of one of the three major coronary arteries. In terms of recovery, there was an increase from 30 per cent to 62 per cent. With respect to irreparable damage to the heart muscle after ligation of a major coronary artery, we can say that abrasion exercises a favorable effect. The infarct caused by acute arterial occlusion is smaller or, indeed, can be altogether prevented from forming in hearts that have been abraded. We can also say that in 32 per cent of the animals the heartbeat was maintained by virtue of the intercoronary communications that developed after the surface of the heart had been abraded. In these dogs infarcts developed; large infarcts developed in many of them. The coronary circulation in these dogs under normal conditions was such that the heart could not have tolerated occlusion of the artery if the circulation had not been aided by the effect of abrasion. After abrasion, the circulation in these hearts was good enough to withstand ligation.

We have shown that, if the heart survives ligation of a major artery, the arterial bed usually becomes a common bed through the medium of intercoronary communications. Coronary occlusion is an effective stimulus to the development of intercoronary channels.

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THE CORONARY OPERATION

CLAUDE S. BECK, M.D.
CLEVELAND, OHIO

THE original idea of revascularization of the myocardium occurred to me in 1931. During the years which have intervened since then, my associates and I have carried out several thousand experiments on dogs' hearts in a study of this and related problems. I have always felt that the surgeon was obliged to prove or demonstrate his point in the laboratory before he tried to apply his idea by operating on the human heart. In several instances, surgeons have gone ahead with operations on the human heart in the hope that the patient would be helped by the operation and that the science would come later. I am critical of this short cut. It is an easy road to take, but it is dangerous and it may be futile. Interest should center first and foremost in experimental demonstration. If experimental demonstration is reasonably acceptable, then we can go to the patient. What we have done on this subject, we have done the hard way. It has been slow and difficult, but we have not applied any idea to the patient that was not investigated first in the laboratory.

I shall refer briefly to some of the facts established by experiment. We established extracoronary communications in grafts. These channels were demonstrated in cleared specimens and were large enough to be seen without magnification. We have not ascertained the direction of flow in these channels, nor have we measured the amount of flow through them. From the scientific point of view it matters little what tissues are used for grafting. The important point is the demonstration of blood vessels. This, I might add, is not a trifling accomplishment if one insists upon the demonstration of blood vessels large enough to be seen without magnification. I feel that, if the graft is going to furnish any significant quantity of blood to the heart, the anastomoses should be large enough to be seen without a microscope. For that reason we gave up the use of watery solutions of dyes for injection purposes, and, in later years, injected our specimens with a mixture of barium sulfate and gelatin. Blood vessels demonstrated by the injection of aqueous solutions may be so small that they may not carry blood. In this respect they are anatomic, but not functional. Vessels injected with the mixture of barium are 40 to 50 micra, or larger, in diameter, and can carry blood. We used many different structures for grafts—parietal pericardium, mediastinal fat, skeletal muscle from the chest wall, lung, omentum brought

From the Department of Surgery, Western Reserve University School of Medicine and University Hospitals of Cleveland.
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up through the diaphragm, spleen, stomach, and bowel. We also used island grafts of internal mammary artery and triangularis sterni muscle. We were the first to use omentum experimentally, but this is not an important consideration. The important point was to produce as many anastomoses as possible, and to make them as large as possible, regardless of the tissue used.

Doctors Tichy, Bright, Mautz, Thornton, Phelps, and Stanton assisted in the study of these problems. We had the belief early in the work that occlusion of the coronary arteries was helpful in the development of anastomoses. To produce occlusion of a coronary artery progressively over a period of time was a problem in itself. Finally and recently, a clamp was devised that could close an artery in four to six weeks by virtue of osmotic pressure. It was shown that, if one of the three major coronary arteries was occluded in stages at successive operations, an infarct did not form. This was an original experimental demonstration. Bright completely occluded the descending ramus of the left coronary artery in stages, and he and Tennant, in Dr. Wiggers' laboratory, showed that the myocardium supplied by this artery maintained its function. It contracted, and did not dilate, as did the myocardium after arterial ligation in the normal, unprepared heart. It was also shown in a few specimens that practically all three major coronary arteries (except the septal artery) could be occluded if the heart had been prepared before the arteries were occluded. We believed that the epicardium was a barrier to the development of extracoronary vessels, and we removed it by various destructive chemical agents, or by a metal burr. We conducted experiments with many foreign bodies on the surface of the heart for the purpose of obtaining an inflammatory reaction. Many of these substances were dangerous, and could not be used on human patients, such as tincture of iodine, Dakin's solution, ether, iron filings, etc. We used powdered beef bone because it produced a mild, foreign-body type of inflammation over a long period of time. Communications were demonstrated between the coronary arteries themselves, and between coronary arteries and arteries of grafted tissues. It was also possible to demonstrate anastomoses extending into the fat at the base of the heart. Anatomic communications normally exist in this fat. They do not carry blood under normal conditions. These channels can be enlarged by surgical methods, and perhaps they can be made to carry blood.

I should like to discuss a point that was learned early in the course of the work which I believe is of importance. It has been published in one of our surgical journals (Annals of Surgery **102**: 801, 1935), but I have not seen it discussed in any of the medical contributions on coronary disease.

When we began to produce coronary obstruction, we did not know whether we should ligate the arteries distally or ligate them close to

their origin from the aorta. A surgical dissection of these vessels at the aorta appeared to present technical difficulties at the time, and we therefore selected peripheral ligation. Four or five small arteries were ligated over the left ventricle, as shown in Fig. 1*b*. I believe we did this experiment about two dozen times before we finally concluded that this was always a fatal procedure. The ventricles went into fibrillation. Then we went up higher on the arteries and placed silver bands on each artery, as in Fig. 1*a*, reducing the cross section of each artery about one-third.

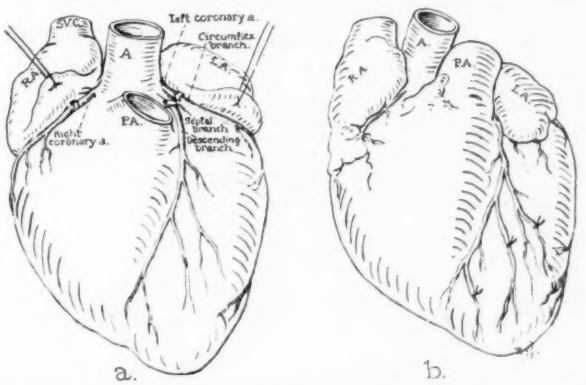

Fig. 1.—Two types of operations are shown: *a* shows the usual sites where silver bands were applied to the coronary arteries. A reduction of 30 to 50 per cent in the cross sectional area of these three arteries was compatible with life. *b* shows another type of experiment. Four or five peripheral branches of the coronary arteries over the apex of the heart were ligated. This experiment was always fatal. In *a* the reduction in total coronary blood flow was considerably greater than in *b*. The heart cannot tolerate ischemia of severe degree, even when the area of ischemia is small. The collateral bed produced by operation can transport blood to such ischemic areas.

The heart could tolerate this degree of obstruction. When one experiment is compared with the other, it would appear that we were dealing with generalized anoxemia in *a*, and localized, but severe, anoxemia of a small part of the myocardium in *b*. I believe the entire coronary circulation was reduced to a greater extent in *a* than it was in *b*, yet recovery took place in *a* and ventricular fibrillation took place in *b*. This experiment made us pay attention to localized anoxemia, and it convinced us that localized anoxemia in the heart was like a trigger that could set off ventricular fibrillation. I believe that the concept of a trigger zone is appropriate, because it implies potential danger to a mechanism that is working smoothly, and, as the clinician well knows, its presence may be entirely unsuspected. We could appreciate this very clearly in the laboratory, and it started us to think about the distribution of blood to the myocardium. We recognized the importance of an equal distribution of blood to all parts of the myocardium, and we came to believe that we could improve distribution of blood by surgical methods. This was accomplished by bringing in blood from the outside through grafts, and also by opening intercoronary channels by producing an inflammatory reaction on the surface of the heart. Both of these developments are important.

Intercoronary communications can be produced in two ways. One is by gradual, progressive occlusion of a major artery. The other is by the production of an inflammatory reaction on the surface of the heart. Both of these demonstrations are original contributions from our laboratory. Abrasion of the surface of the heart is effective in opening intercoronary communications. Foreign bodies and chemical agents are also effective. Each of these methods can function in a mutually complementary manner, as I shall try to show. We can readily understand how a trigger zone develops in the myocardium because of arterial disease. Anything in the way of improved distribution in the early stage of the disease will delay or remove the threat of ventricular fibrillation. The opening or the development of new, intercoronary communications in the early stages of the disease should be able to accomplish this. The intercoronary communications develop as the occlusive process develops. It is obvious that catastrophe can be delayed by the presence of a common coronary bed. It is reasonable to believe that surgical methods are effective in the production of a common bed.

The coronary problem was studied over a three-year period before any application to the human heart was attempted. Dr. Harold Feil selected thirty patients for operation. They were to constitute a study group. The operation was not looked upon as a matter of therapy. The first operation was performed on Feb. 13, 1935; the last in this study group was performed on April 19, 1938.

The first requirement in the selection of the patient for operation was that he should be severely crippled by the disease. We did not accept anyone who could get along moderately well with bed rest and drugs, and no one who could hold down any kind of job was taken. We did not desire to take patients who had circulatory failure. However, one patient had severe edema and dyspnea at the time of operation. The point that I should like to make is that we did not feel justified in taking patients who seemed to have a chance to keep on living, and each patient felt that he was facing imminent catastrophe without operation.

A follow-up report of results was presented to the American Association for Thoracic Surgery, in 1940, by Dr. Feil, and was published in the journal of that association (**10**: 529, 1941). As I look at this part of the work at its present stage of development, I can see that certain considerations are of greater importance than others. I would not give a place of first importance to such considerations as selection of patients, details of operation, whether omentum or something else should be used, and mortality. I believe the most important question is this: Has operation helped anyone in the group? The answer to this question determines whether or not medical methods of treatment of coronary disease will prevail without exception, or whether operations will be performed upon some of these patients. The second important question is this: What is

the best result from operation in the group? The answer to this question provides a measurement of the best that operation can give—a standard of attainment, so to speak. The third question is: What is the explanation of the clinical improvement? The answer to this will tend to keep the operative technique on a scientific basis. If surgery finds a place in the treatment of coronary disease, the technique will undergo changes. Someone will advocate the use of a foreign body only, without grafts, as I did in the thirteenth patient of our series five years ago. This patient had circulatory failure, and it appeared that he would not stand much in the way of an operation. We opened the pericardium and introduced powdered beef bone to obtain an inflammatory (foreign body) reaction on the surface of the heart without using any grafts. Someone will conceive the idea of injecting a chemical agent, such as sodium morrhuate, sodium ricinoleate (or croton oil, which should never be used) into the pericardial cavity without exposing the heart and without operation. I should like to repeat here that all procedures should be tested in the laboratory before they are applied to patients. Many substances cannot be tolerated and will cause death.

In answer to the first question, I can say that, with exceptions, the operation is beneficial. Ten of the thirty patients died during the immediate postoperative period. All of these patients had severe coronary disease, as shown by necropsy examination. I do not believe that the operation in itself need be more severe or shocking than any ordinary operation. Of the twenty patients who were discharged from the hospital, sixteen are still living and four are dead. Every one of the sixteen has been improved, and twelve of them have what Dr. Feil calls a good result.

It is a pleasure for me to answer the second question. The degree of benefit has been great. Indeed, it is almost incredible. The first patient in the series was operated upon six years ago. Four months after operation he got a job as a gardener. For the past four years he has worked as a farm hand. He has no symptoms. The second of those now living is a surgeon. He was operated upon six years ago. He believes the operation saved his life. He also believes that the operation should be applied as a matter of therapy. The list of patients includes several salesmen, several machinists, a factory superintendent, a school teacher, a painter, a cook, a clerk, a coal miner, a waiter, and a moulder. Not all are back at work, but many of them are, and every one of them states that he is better than he was before the operation. I have asked Dr. Feil whether results like this could occur in a group of similar patients who were not operated upon. He states that it is unusual for a patient, after he has had a coronary thrombosis, to recover to such an extent that he can resume manual labor and be able to work for a period

of several years. Although this might occur in unusual instances, a group experience such as this, he states, does not occur.

I believe the scientific explanation for the improvement in our group of patients can be given in a fairly reasonable manner. We have been fearful to accept the beneficial result obtained in the patients until we demonstrated that abrasion of the heart was a more important factor than we appreciated in the past. Up to this time the clinical result was better than our laboratory demonstrations could explain satisfactorily. We could not understand why many of the patients stated that they felt better as early as one week after the operation. The earliest that we could demonstrate injection across the grafts, using watery solution of dye, was two to three weeks, and we did not believe that the circulation through the grafts could provide such early improvement. I can accept the explanation now that intercoronary communications were opened by the abrasion, and that this explains the early improvement which was noted so frequently. Some of the patients showed continuing improvement after a two-year period. We do not know what will happen to extracoronary communications in the course of years, whether they will increase or diminish in size. The relative importance of intercoronary and extracoronary communications remains to be ascertained. In the best of the three human hearts that we examined, we found that the mixture of barium sulfate and gelatin which was injected into the coronary arteries escaped through the grafts. The transfer was through about ten or twelve anastomoses that could be seen in the cleared specimen without magnification. Intercoronary channels were also present, and these could have been developed by the operation or by the progressive narrowing of the coronary arteries higher up. Additional information on this will be obtained in the future.

Up to the present time I have considered the work as an experimental study, and I have advised against accepting it as a matter of therapy. The experiments by Stanton, Schildt, and myself are encouraging, as are also the experiments by Heinbecker and Barton, of St. Louis. It appears to me that we should continue to regard the work as an experimental study, and not as a matter of therapy. I do not believe that the operation is ready for surgeons to take up generally. However, I should like to solicit the help of the American Heart Association in selecting a number of patients who are willing to have the operation done, so that a preliminary appraisal of results can be made by people other than ourselves. I believe that it would be advisable to carry out the operation on 100 patients as a preliminary study, before deciding the question of therapy. I should be pleased to do these operations because the technical aspects of the operation should be controlled. Cooperation in this preliminary study is needed.

SYMPATHECTOMY AND EXPERIMENTAL OCCLUSION OF A CORONARY ARTERY

ARNALDO YODICE,* M.D.
BUENOS AIRES, ARGENTINA

THE purpose of this paper is to record experiments in which the sympathetic nerves to the heart were removed and a major coronary artery was ligated. Leriche, Herrmann, and Fontaine[1, 2] maintained that removal of the sympathetic nervous system protected the heart when the descending ramus of the left coronary artery was ligated. This conclusion was based upon four experiments. Cox and Robertson[3] asserted that the mortality was reduced from 50 to 10 per cent after ligation of this artery in the normal heart if the stellate ganglia had been removed before the ligation. They also stated that the infarct caused by ligation of the artery was smaller if the stellate ganglia were removed before ligation. Mendlowitz, Schauer, and Gross[4] pointed out that the heart rate became slower after removal of the sympathetic chain, but this bradycardia was only temporary. Bilateral sympathectomy produced fatal heart block in a few of their experiments. Schauer, Gross, and Blum[5] reported measurements of cardiac output, circulation time, and arterial pressures in animals after ligation of the descending ramus of the left coronary artery. In some experiments the stellate ganglia were removed before the artery was ligated. In both types of experiments there were a fall in cardiac output, a delay in the circulation time, and a fall in blood pressure. Sympathectomy reduced the incidence of ventricular fibrillation and the mortality rate after arterial ligation. The size of the infarct was the same in both types of experiments.

My interest in repeating these experiments was to ascertain whether the effect of sympathectomy was sufficiently beneficial to apply the procedure in the treatment of coronary sclerosis.

EXPERIMENTS

The stellate ganglia and the sympathetic chain down to the eighth, ninth, or tenth rib were removed on both sides. The left coronary artery was dissected at its bifurcation into the ramus circumflexus and the ramus descendens. The latter was isolated, doubly ligated, and cut. This high level for ligation of the artery was selected in each experiment. The operations were carried out under ether anesthesia.

In one series of experiments this procedure on the sympathetic nervous system was completed and was followed by ligation of the artery at the

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Docente Libre de Patologia Quirurgica y de Clinica Quirurgica cirujano y Jefe de Clinica del Hospital Ramos Mejia, Buenos Aires.
*Visiting Fellow, University Hospitals and Laboratory of Surgical Research, Western Reserve University, Cleveland.

same operation. In the other series of experiments, an interval of eleven to twenty-five days (average, about seventeen days) elapsed between removal of the sympathetic system and ligation of the artery. The results of these experiments are given in Tables I and II.

TABLE I

DOG	INTERVAL BETWEEN SYMPATHECTOMY AND LIGATION OF CORONARY ARTERY (DAYS)	RECOVERED	DIED
1	11		1 day
2	17	Killed after 3 mo.	
3	17		1 day
4	16		2 days
5	25		1 day
6	17		4 hours
7	16		7 days*
8	19		1 day
9	17	Killed after 53 days	
10	20		1 day
11	20		5 min.
12	19	Killed after 48 days	
13	17		2 hours
14	17		12 min.
15	17		3 days*
16	17		30 min.

Bilateral sympathectomy and ligation of descending ramus of the left coronary artery at its origin were done in two operations.

*Two animals had pneumonia (Experiments 7 and 15).

TABLE II

DOG	RECOVERED	DIED
1		5 min.
2		1 day
3		6 days*
4		7 days*
5	Killed after 23 days	
6	Killed after 23 days	
7		2 days*
8		10 min.
9	Killed after 44 days	
10	Killed after 44 days	
11	Killed after 43 days	
12		1 day
13		2 days*
14		1 day
15		4 days*
16		10 min.
17		1 day
18	Killed after 38 days	

Bilateral sympathectomy and ligation of descending ramus of left coronary artery at its origin were done at the same operation.

*Pneumonia was found in Experiments 3, 4, 7, 13, and 15.

The control experiments consisted of ligation of the artery only. This group of experiments was done by Beck and Mako,[6] in this laboratory (Table III).

In ten experiments, procaine was applied to the surface of the heart before and after the descending ramus of the left coronary artery was

ligated. Two cubic centimeters of a 5 per cent solution of procaine, when applied to the epicardium, produced slowing of the heart rate and reduced the responses of the heart to mechanical, electrical, and chemical stimuli. This drug was applied both before and after ligation of the artery. In a series of ten experiments, five animals survived ligation and five died. In two experiments, ventricular fibrillation occurred a few minutes after ligation of the artery; two animals died on the first day, and one died on the second day after ligation. The application of procaine to the surface of the heart did not prevent ventricular fibrillation after the artery was ligated. The fact that five of ten dogs survived suggests that the drug may have a beneficial effect, but, if so, it is slight.

TABLE III

	DOG	LIVING	DEAD
	10	1	9
	10	2	8
	10	3	7
Total	30	6—20%	24

Control experiments in which the descending ramus of the left coronary artery at its origin was ligated. Analysis of deaths shows that seven died 5 to 30 minutes, fifteen, 2 to 18 hours, one, 15 days, and one, 18 days, following ligation.

The size of the heart was ascertained before and after operation by means of standardized roentgenograms. These were taken with a constant target-film distance. According to these measurements, the size of the heart was the same before and after sympathectomy.

The size of the infarcts was ascertained after serial, transverse incisions across the ventricles were made. An infarct was found in every experiment in which the dog survived arterial ligation, and the infarcts were about the same in each group of experiments.

DISCUSSION OF RESULTS

In one series of sixteen experiments the sympathetic nervous system was removed, and, about seventeen days later, the descending ramus of the left coronary artery was ligated. In this series recovery took place in three instances, or about 20 per cent, and death occurred in thirteen, or 80 per cent. This mortality rate is about the same as that in the control group. If the cause of death could be attributed to pneumonia in Experiments 7 and 15, the mortality rate would be changed in no significant degree. These experiments indicate that sympathectomy does not reduce the mortality rate when the descending ramus of the left coronary artery is ligated, provided the interval between the two operations is about seventeen days.

In a series of eighteen experiments the sympathetic nervous system was removed, and, at the same operation, the descending ramus of the the left coronary artery was ligated. In this series recovery took place in six instances, or about 33 per cent, and death occurred in twelve, or

66 per cent. This mortality rate is somewhat less than that in the control group. The difference, however, may be of no significance. Pneumonia was found at autopsy in five dogs. It is probable that this complication was responsible for the death of one or more of these animals. If pneumonia, instead of arterial ligation, were the responsible factor in all of these experiments, the recovery rate would be increased to about 60 per cent. Ventricular fibrillation occurred in three of the eighteen experiments in the course of minutes after arterial ligation. This is about the same incidence as in the control group, namely, seven of thirty experiments.

CONCLUSIONS

1. Sympathectomy does not reduce the mortality of coronary arterial ligation, provided an interval of about seventeen days is allowed to elapse between the two operations.

2. Sympathectomy followed immediately by arterial ligation carries a slightly lower mortality than arterial ligation alone. This beneficial effect is transient. It is slight in degree, and, indeed, it may be questionable as to whether it exists. The heart is less irritable and the rate of contraction is slower after sympathectomy. In this respect the effect of sympathectomy resembles the effect of applying procaine to the surface of the heart.

3. The size of the infarcts caused by arterial ligation is not reduced by sympathectomy.

4. These studies indicate that sympathectomy cannot be considered an effective method of reducing mortality or size of infarcts resulting from acute coronary occlusion. It may have a slightly beneficial effect, but this effect, if present, is transient.

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Special Article

NOMENCLATURE

Diseases and Abnormalities of the Blood and Lymph Vessels of the Extremities

DISEASES OF ARTERIES AND ARTERIOLES

I. Functional (vasomotor) conditions

A. Vasoconstrictor

1. Raynaud's syndrome (primary or idiopathic) (late stages secondary organic changes in arteries, skin, and subcutaneous tissues)
2. Raynaud's syndrome (secondary)
   a. Traumatic vasospastic syndrome—pneumatic hammer disease, other types of repeated trauma.
   b. Neurogenic—cervical rib, scalenus anticus syndrome, spondylitis, neuritis
   c. Secondary to organic vascular disease—arteriosclerosis, thromboangiitis obliterans, syphilitic arteritis
   d. Intoxications—nicotine, arsenic, ergot (early) lead?
   e. Miscellaneous
3. Acrocyanosis
4. Cutis marmorata (early livedo reticularis)
5. Vasospasm secondary to
   a. Lesions of peripheral nerve, brain, spinal cord
   b. Thrombophlebitis
   c. Acute arterial occlusion
   d. Post-traumatic osteoporosis

B. Vasodilator

1. Erythromelalgia (erythermalgia)—primary
2. Erythromelalgia (erythermalgia)—secondary to
   a. Polycythemia vera
   b. Arteriosclerosis
   c. Thromboangiitis obliterans
   d. Trauma
   e. Miscellaneous—secondary to fever, hyperthyroidism, alcoholism, neurocirculatory asthenia, menopause

II. Organic (structural) conditions
- A. Occlusive (organic)
  1. Generalized arteriosclerosis
     - a. Arteriosclerosis obliterans
     - b. Medial (Mönckeberg's) arteriosclerosis
     - c. Combined
  2. Thromboangiitis obliterans
  3. Periarteritis nodosa (essential periarteritis)
  4. Temporal arteritis
  5. Ergotism (early stages may be spastic)
  6. Arteritis and arteriolitis secondary to
     - a. Infectious diseases
     - b. Local inflammatory processes
     - c. Hypertension
     - d. Lupus erythematosus disseminatus (including Libman-Sachs syndrome)
     - e. Idiopathic
  7. Simple arterial thrombosis
     - a. Associated with infectious diseases
     - b. Associated with blood dyscrasias
     - c. Secondary to trauma or compression
     - d. Idiopathic
  8. Abscess of the wall of artery (state organism)
  9. Frost bite
  10. Pernio
  11. Livedo reticularis
  12. Arterial embolism
      - a. Blood thrombus
      - b. Fat
      - c. Air
      - d. Bacterial
      - e. Neoplastic
      - f. Fungous
      - g. Inorganic substances
- B. Nonocclusive
  1. Aneurysm
     - a. Congenital
     - b. Syphilitic
     - c. Arteriosclerotic
     - d. Mycotic
     - e. Traumatic
     - f. Idiopathic
  2. Arteriovenous fistula
     - a. Congenital
     - b. Traumatic

c. Secondary to malignancy or other disease
d. Mycotic
3. Congenital anomalies—other than fistula
4. Trauma and external compression (scalenus anticus syndrome)
5. Rupture
6. X-ray, radium, telangiectasia

NOTE. Ulceration or gangrene, when present, should be noted.

DISEASES OF VEINS

I. Vasomotor (functional)
Spasm
Following injury or disease of vein or accompanying artery or nerve

II. Organic (structural)
A. Obstructive
1. Thrombophlebitis and venous thrombosis (phlebothrombosis)
a. Primary
1. Thromboangiitis obliterans
2. Recurrent or migrating (without arterial lesions)
3. Essential
b. Secondary to
1. Mechanical injury (contusion, laceration, surgery)
2. Muscular effort or strain
3. Chemical injury (sclerosing agents, drugs, solutions for diagnosis)
4. Inflammatory or suppurative lesions—Infectious diseases
a. Tuberculosis, syphilis, actinomycosis
b. Other bacteria (to be specified)
5. Severe ischemia
6. Chronic disease of vein wall (varices, phlebosclerosis) (Late complications—varicose or post-phlebitic ulcers)
7. Blood dyscrasias (polycythemia vera, leucemia, pernicious anemia)
8. Epidermophytosis (?)
2. Neoplastic invasion of vein
3. Venous compression, with or without thrombosis or thrombophlebitis, due to
a. Gravid uterus
b. Neoplasm
c. Aneurysm
d. Scar tissue
e. Scalenus syndrome
f. Fractures and dislocations
g. Increased intra-abdominal pressure (ascites, etc.)

B. Nonobstructive
   1. Varicose veins (aneurysm)
      a. Primary—congenitally incompetent valves
      b. Secondary (to proximal obstructive lesions or pressure)
      c. Secondary to phlebitic destruction of valves
      d. Compensatory dilatation of collateral veins
   2. Arteriovenous fistula
      a. Congenital
      b. Traumatic
      c. Mycotic
      d. Secondary to local disease
   3. Aberrant position
   4. Hypoplasia
   5. Phlebectasia
   6. Periphlebitis without thrombosis
   7. Phleboselerosis (not usually obstructive)
   8. Rupture

TUMORS OF BLOOD VESSELS

A. Hemangioma
   1. Simplex-telangiectasis
      a. Nevus cinosus
      b. Plexiform angioma
      c. Hemangioma hypertrophicum
         1. Klippel-Trenaunay syndrome (hemangioma, varicose veins, osteohypertrophy)
   2. Cavernosum
   3. Racemosum (capillary)
B. Hypertrophic granulation tissue
C. Hemangio-endothelioma
D. Angiosarcoma
E. Glomus tumor
   1. Leiomyoma of vessel wall
F. Endothelioma
G. Endothelial myeloma
H. Kaposi's disease
I. Sarcoma of blood vessel sheath

TUMORS OF LYMPH VESSELS AND LYMPH TISSUES

A. Lymphangioma
   1. Simplex
   2. Cavernosum
   3. Cysticum (hygromas)
   4. Secondary to incompetent valves

B. Endothelioma
C. Lymphoma (benign)
D. Lymphocytoma
E. Leucemia
F. Lymphosarcoma
G. Hodgkin's disease
H. Reticulum cell sarcoma
I. Sarcoma of sheath or capsule of lymph node

DISEASES OF PERIPHERAL LYMPH NODES AND LYMPH VESSELS

I. Vasomotor (functional); none established
II. Organic (structural)
  A. Obstructive
    a. Noninflammatory
      1. Primary lymphedema
        a. Simple
        b. Congenital
        c. Hereditary (Milroy's disease)
        d. Precox
      2. Secondary lymphedema due to
        a. Surgical removal of lymph nodes
        b. Neoplastic invasion of lymph nodes
        c. X-ray treatment
    b. Inflammatory
      1. Primary lymphangitis (cause unknown)
      2. Secondary lymphangitis due to
        a. Filariasis
        b. Trichophytosis
        c. Local tissue injury or inflammation (lacerations, bites, burns, furuncles, other local infections, chemical, non-bacterial)
      3. Erysipelas
    c. Calcification and fibrosis
    d. Chylous ascites—secondary to obstruction of the thoracic duct (mention cause)
  B. Nonobstructive
    a. Lymphatic fistula
    b. Unclassified

DISEASES OF MINUTE VESSELS

A. Increased fragility
  1. Infectious purpura
    a. Pneumonia
    b. Septicemias, especially streptococcus

c. Exanthemata
d. Other infectious diseases

2. Toxic purpura
   a. Arsenic
   b. Phosphorus
   c. Phenolphthalein
   d. Numerous other drugs (individual susceptibilities)
   e. Snake venom—insect venom
3. Purpura due to avitaminosis C.K. (P.?)
4. Hematogenic purpura
   a. Thrombocytopenia
   b. Leucemia
   c. Aplastic anemia
5. Purpura secondary to increased venous pressure
6. Menstrual or menopausal purpura
7. Senile purpura
8. Idiopathic purpura
   Henoch's purpura
   Schoenlein's purpura

B. Increased permeability
1. Angioneurotic edema
2. Urticaria
3. Sensitivity to physical agents
   a. Mechanical irritation
   b. Cold
   c. Heat
4. Local inflammation
5. Vasomotor collapse
6. Shocks
7. Burns

CLASSES ACCORDING TO SEVERITY

Class 1. Without symptoms
2. With symptoms—without organic changes
3. With symptoms—with organic changes
4. With loss of substance, trophic changes, gangrene, ulceration, etc.

The Nomenclature Committee of the Section for the Study of the Peripheral Circulation of the American Heart Association has prepared the first section of the Nomenclature of Diseases and Abnormalities of the Blood and Lymph Vessels. This section includes the blood and lymph vessels of the extremities only. The Committee has been aided by the advice and constructive criticism of all the Fellows of the Section and numerous other authorities in special divisions of the field.

Acknowledgment is especially due to the Executive Committee of the American Society for the Control of Cancer, which, under the Chairmanship of Dr. Frank Adair, compiled the subdivisions entitled "Tumors of the Blood Vessels" and "Tumors of the Lymph Vessels."

This Section is published at this time in order to provide a list of preferred and universal terms which may be used by authors, research workers, and all others interested in this field. It is recognized, however, that any nomenclature of this nature must be continuously regarded as in a fluid state, subject to frequent revision, and that this is not considered by the Committee to be a final listing.

The second section of this Nomenclature, including hypertension, nephritis, and associated diseases will continue in a state of preparation. The rapid changes taking place in the conceptions of the mechanisms involved in these diseases make it appear unwise to publish even a tentative nomenclature at this time. It is thought that several more years of study may well be needed for this problem, and, therefore, although the committee firmly believes that these two sections of the nomenclature should ultimately comprise a single integrated conception of diseases and abnormalities of the circulation, it will be helpful to present the section which has been most nearly completed at this time.

Nomenclature Committee of the Section for the
Study of the Peripheral Circulation of the
American Heart Association.

Irving S. Wright, M.D., Chairman
M. Herbert Barker, M.D.
Nelson W. Barker, M.D.
Norman Freeman, M.D.
William Goldring, M.D.
E. A. Hines, M.D.
Irvine H. Page, M.D.
Gerald H. Pratt, M.D.
Milton C. Winternitz, M.D.

Department of Clinical Reports

PRIMARY SARCOMA OF THE HEART

Report of a Case

David R. Weir, M.D., and Benjamin C. Jones, Jr., M.D.
Cleveland, Ohio

PRIMARY sarcoma of the heart occurs rarely enough to make the report of another case worth while. Diebold,[1] in 1930, and Yater,[2] in 1931, found forty-six cases in the literature. Twenty-nine additional cases were reported between 1930 and January, 1940, making a total of seventy-five cases. The diagnoses are given in Table I.

Table I

DIAGNOSIS	NO. OF CASES
Spindle cell sarcoma[2-4]	17
Fibrosarcoma[2, 5-7, 27]	7
Leiomyoblastic sarcoma[8]	1
Rhabdomyosarcoma (?)[9]	1
Angiosarcoma[2, 10, 11]	5
Myxosarcoma[2, 12, 13]	6
Round cell sarcoma[2, 14-18]	19
Mixed cell sarcoma[2, 19]	5
Giant cell sarcoma[2]	4
Lymphosarcoma[2, 20]	2
Unclassified sarcomas[2, 21-26]	8
Total	75

Under angiosarcoma are included the two cases of Choisser and Ramsey[11] which they regard as instances of typical Kaposi tumors and have called angioreticuloendotheliomas. They believe that careful review of the microscopic sections in all reported cases would disclose other tumors that could be put into the same classification.

Larson and Sheppard's[9] case of rhabdomyosarcoma in a 37-year-old woman is the only one of several which have been reported in which reasonably good photomicrographic evidence is presented to confirm that diagnosis. However, even in their case the evidence is not unequivocal.

In the twenty-eight cases which have been reported since 1930, the site of origin was mentioned in twenty-four. In twelve of these the tumor arose from the right auricle. This corroborates Yater's[2] statement that the right auricle is by far the most common site of origin. The presence or absence of metastases was noted in twenty-one of the

From the Department of Medicine and the Institute of Pathology, University Hospitals, and Western Reserve University.
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twenty-eight cases, and thirteen of these twenty-one showed definite metastases. Diebold and Yater found that metastases were noted in only fifteen of their forty-six cases.

CASE REPORT

A 60-year-old white man entered the Lakeside Hospital complaining of dyspnea of eight weeks' duration. For nine years before entry he had come on numerous occasions to the Outpatient Department complaining of a variety of seemingly neurotic symptoms. Except for slight hypertension (168/98), which was discovered eight years before admission, there had been no abnormal physical signs. About eight weeks before admission he began to have definite shortness of breath on exertion, without orthopnea or paroxysmal nocturnal dyspnea. This was associated with slight precordial pain. Two electrocardiograms which were taken at that time showed left axis deviation, but no evidence of myocardial infarction. The dyspnea continued, and he gradually developed cough and loss of appetite. Four weeks before entry the cough became productive of bloody sputum, and râles were heard at the bases of the lungs. A roentgenologic examination five days before admission showed small areas, measuring up to 2 cm. in diameter, of increased density scattered throughout both lungs.

At the time of admission to the hospital, physical examination revealed a well-developed, well-nourished white man who was having moderate respiratory distress. There was slight cyanosis of the lips and finger tips. The heart was somewhat enlarged to the left, and the aortic second sound was accentuated. No significant murmurs were heard. Scattered patches of râles were heard throughout both lungs. The breath sounds were diminished over the left apex posteriorly, but there was no evidence of consolidation of the lungs. The edge of the liver was slightly tender and was palpable 2 cm. below the costal margin. The abdomen was otherwise normal. The prostate was moderately enlarged, symmetrical, and without nodules. There was no fluid in any of the body cavities, and no peripheral edema was present.

The temperature was 37.7° C.; the pulse rate, 100; the respiratory rate, 23; and the blood pressure, 134/70.

The urine was normal. The erythrocyte count was 3,330,000; the hemoglobin was 66 per cent, and the leucocyte count was 12,250, with 77 per cent polymorphonuclear leucocytes. The Kline exclusion test was negative. The blood urea nitrogen was 21 mg. per 100 c.c. Smears of the sputum showed a variety of cocci and many budding, yeastlike organisms. The sputum cultures yielded yeasts, *Streptococcus hemolyticus*, *Streptococcus viridans*, and *Staphylococcus albus*.

A roentgenologic examination of the chest on the first hospital day showed a questionable increase in the size of the lesions in the lungs, and it was thought that many of the lesions had a distinctly nodular appearance.

On the day after admission, auricular fibrillation set in, with a ventricular rate of 104 and a radial pulse rate of 80. The diagnosis was confirmed by an electrocardiogram. The following morning at 9 o'clock, the auricular fibrillation was still present. At about 11 A.M. the patient suddenly became extremely dyspneic. The pulse rate was found to be 180 and the pulse was regular. An electrocardiogram showed auricular flutter. In spite of emergency measures he died about twenty minutes after the onset of the flutter.

POST-MORTEM EXAMINATION

The essential autopsy observations were limited to the heart, lungs, and adrenals.

The heart was firmly adherent to the pericardium; together, they weighed 970 Gm. From the medial and anterior aspects of the wall of the interior of the right

atrium there arose a large, firm, yellowish-brown papillary tumor which completely filled the right auricular appendage, extended over the anterior leaflet of the tricuspid valve, and up the superior vena cava as far as the ostium of the left subclavian vein. The main tumor measured 10 × 3 × 2.5 cm. and had invaded the myocardium of the auricles and right ventricle. There was no endocarditis or valvulitis.

The parenchyma of both lungs was studded with innumerable discrete and confluent grayish-purple nodules of tumor tissue, measuring up to 2 cm. in diameter. No single, large, tumor mass was found in either lung, and no nodules were seen arising from the larynx, trachea, or bronchi.

The medulla of each adrenal was infiltrated by tumor tissue, which, in one, measured 2 cm., and, in the other, 1.5 cm. in diameter.

Microscopic Examination.—Sections through various portions of the tumor, stained with hematoxylin and eosin, showed small groups, slightly whorled and interlacing cords, and solid sheets of cells. The cells were supported by a moderate amount of stroma. There were extensive invasion and destruction of the myocardium and epicardium. Many small and large areas of necrosis and hemorrhage were present. From place to place throughout the tumor there was striking pleomorphism. However, the predominating type of cell was of moderate size, elongated, with homogeneous acidophilic cytoplasm. The nuclei were round or oval and occupied from one-third to one-half of the cell volume. They were vesicular and contained a fine network of chromatin and one or two indistinct nucleoli. Numerous normal mitotic figures were present, but there were no multinucleated cells. In some areas the cells were completely undifferentiated and resembled both epithelium and reticulum cells. In other areas they were predominantly spindle-shaped, with sausage-shaped nuclei, long, tapering, cytoplasmic processes, and parallel bundles of extracellular fibrils. Scattered throughout the tumor were a few large cells with vesicular, hypochromatic nuclei. These contained intracellular fibrils, as shown by the phosphotungstic acid hematoxylin stain, and resembled myoblasts.

Sections stained by the van Gieson and azocarmine methods showed that the supporting stroma of the tumor contained only a small amount of collagen. Sections of the tumor stained by the phosphotungstic acid hematoxylin method failed to reveal cross striations in any of the tumor cells.

Microscopic examination of the tumor nodules which were found in the lungs and adrenals showed that they were histologically identical with those in the heart. Throughout the lungs, tumor was found in the peribronchial tissues and, in several sections, was found to have grown through the bronchial wall into the lumen. In these areas there was slight hemorrhage into the bronchi.

A clinical diagnosis of carcinoma metastatic to the heart and lungs, primary source undetermined, was made. The tumor was thought to involve the heart because of the unexplained cardiac failure and the appearance of auricular fibrillation and auricular flutter for no apparent reason. Except for mild hypertension, no clinical evidence of the common forms of heart disease could be found.

The largest tumor was in the right atrium. The direct and irregular invasion of neighboring structures was more like the growth of a primary than a secondary tumor of this region. The focalized, nodular character of the tumors in the lungs and adrenals was what would be expected of metastatic lesions. The tumor was histologically the same everywhere. The gross and microscopic character of the various lesions indicated that the tumor was primary in the heart. The involvement of the lungs and of the two adrenals was caused by blood vascular dissemination.

The sarcomatous nature of the neoplasm was evident. The absence of cross striations and the fact that no rods were found in the large, spherical cells excluded

rhabdomyomatous tumor. Because of the presence of fibrils, which were like myofibrils, because of the fibrillar content of the cytoplasm of the large, spherical cells, and because of the nuclear forms in the elongated cells, Dr. Howard T. Karsner classified this sarcoma as a leiomyosarcoma. This view was shared by several other experienced pathologists who saw the material, but not by one pathologist, who believed that it was a mesothelioma. Although it undoubtedly originated in the right atrium, the exact point of origin could not be ascertained.

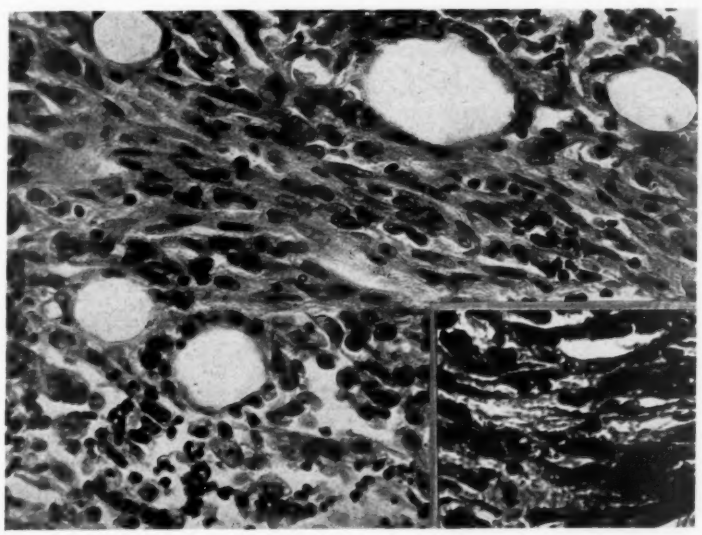

Fig. 1.—Larger field shows invasion of epicardial fat by tumor made up of elongated cells with "sausage-shaped" nuclei. Cytoplasm shows barely visible longitudinal fibrils. Hematoxylin and eosin (×450). Smaller field shows, in the middle, definite longitudinal fibrils. Phosphotungstic acid hematoxylin (×540).

COMMENT

The clinical diagnosis of primary or secondary tumor of the heart has been made fairly frequently in recent years. The majority of these diagnoses were made by means of the following criteria, as summarized by Yater and others: unexplained congestive heart failure, unexplained electrocardiographic changes, such as heart block and nodal rhythm, unexplained auricular fibrillation and auricular flutter, signs of acquired pulmonic stenosis, other signs of obstruction of blood flow through the heart without obvious cause, failure to respond to digitalis, bloody pericardial effusion, and roentgenologic evidence of irregularities of the cardiac shadow. When a primary malignant tumor is known to exist elsewhere in the body, metastatic involvement of the heart may be more readily suspected when some of the above manifestations are present.

SUMMARY

This case of primary sarcoma of the heart brings to seventy-six the total number of cases of this disease now on record. This includes

two cases in which the tumor was regarded as an angioreticuloendothelioma. Various signs and symptoms led to a correct clinical diagnosis of cardiac neoplasm.

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Department of Reviews and Abstracts

Selected Abstracts

Graybiel, A., and White, P. D.: Diseases of the Heart. A Review of Significant Contributions Made During 1940. Arch. Int. Med. 67: 1061, 1941.

This is the annual review of diseases of the heart in this journal. Particular emphasis is given to the medical problems associated with the World War, especially the examination of the heart in the selection of military personnel. Attention is directed also to neurocirculatory asthenia.

McCULLOCH.

Boyd, T. E., and Patras, Mary C.: Variations in Filling and Output of the Ventricles With the Phases of Respiration. Am. J. Physiol. 134: 74, 1941.

A method of cardiometric recording, designed for use with the chest closed, is described. It maintains on the ventricles an external pressure which is always approximately equal to intrathoracic pressure, varying in the normal manner with the phases of respiration. It can be alternatively used in such a way that the ventricles are left under constant atmospheric pressure.

With the ventricles under atmospheric pressure, diastolic volume and stroke output diminish markedly with inspiration (confirming the findings of earlier investigators). These are abnormal effects, due to the artificially high resistance against which the ventricles are filled.

With the ventricles under intrathoracic pressure, combined diastolic volume and stroke output of the two ventricles are augmented with inspiration. These effects are most pronounced when inspiration is deep and prolonged. They are relatively small in quiet eupneic breathing and are minimal when breathing is rapid and shallow.

AUTHORS.

Keys, A.: Estimation by the Foreign-Gas Method of the Net (Systemic) Cardiac Output in Conditions Where There Is Re-Circulation Through the Lungs. Am. J. Physiol. 134: 268, 1941.

Some fundamental kinetics have been analyzed for the gas absorption by the blood in the foreign-gas methods for estimation of the cardiac output in man. The discussion applies specifically to the acetylene method but the conclusions apply to the other foreign gases.

It is shown that the absorption proceeds according to an equation of the first order, and the mathematical analysis is developed accordingly.

The condition where recirculation occurs in the lungs is analyzed in detail, and equations are derived for the proper computation of the true systemic circulation in such cases. The variables involved are the concentrations of the foreign gas in the gas samples from the lung-bag system, the fraction of blood recirculated, the short-circuit time, and the total time between samples. Graphs for computations with these variables are presented.

It is shown that recirculation through the lungs in the presence of patent ductus arteriosus or interventricular septal defects does not necessarily introduce a serious error and that this error may be estimated.

It is shown that recirculation of blood from the coronary system cannot introduce an appreciable error.

The error resulting from the common assumption that the absorption of the foreign gas is linear with time is discussed and shown to be ordinarily small. Means are provided to estimate this error by equations and a graph.

Timing of the gas sampling is discussed. It is shown that the second sample may be taken later than is frequently believed possible. When there is recirculation, the first sample should be delayed four to five seconds, but it is shown that two to three seconds are not critical.

Results of forty-one studies on twenty-two patients with patent ductus arteriosus are presented in summary form. The average cardiac index is normal or close to it in this group.

It is indicated that many criticisms of the foreign-gas methods are invalid because they are based on quantitative misconceptions. On the other hand the importance and difficulty of physiologic standardization in cardiac output measurements are frequently underestimated.

AUTHOR.

Holt, J. P.: The Collapse Factor in the Measurement of Venous Pressure. The Flow of Fluid Through Collapsible Tubes. Am. J. Physiol. **134**: 292, 1941.

Right auricular and peripheral venous pressures were measured in dogs breathing from a chamber in which the pressure varied between 20 cm. of water above atmospheric and 20 cm. below. It was shown that, when auricular pressure was decreased greatly, and in some cases when auricular pressure was increased slightly, the peripheral venous pressure remained constant. In most cases when auricular pressure increased, the peripheral venous pressure was increased.

The flow of water through collapsible tubes such as the jugular vein of the dog was studied in a model. When fluid is flowing through a partially collapsed tube, increasing the pressure on the upstream side of the partially collapsed segment decreases the resistance to flow through the collapsible segment and increases the rate of flow, whereas lowering the pressure on the downstream side of the collapsible segment increases the resistance to flow through the collapsible segment and either does not change the rate of flow or decreases it slightly. An increase in the jacket pressure around the collapsible tube increases the resistance to flow through the collapsible segment and decreases the rate of flow.

As a collapsible tube, having fluid flowing through it, starts to collapse, it pulsates; as it becomes more collapsed, the pulsation increases in rate; and on further collapse the pulsation apparently disappears.

The length of the collapsible tube is not important in controlling the length of the partially collapsed segment. It appears to be necessary only that the tube be long enough and relaxed enough to collapse in order to give the results described, and any length of collapsible tube greater than this length acts merely as a dilated or rigid tube.

AUTHOR.

Pitts, R. F., Larrabee, M. G., and Bronk, D. W.: An Analysis of Hypothalamic Cardiovascular Control. Am. J. Physiol. **134**: 359, 1941.

Stimulation of the hypothalamus of the anesthetized cat with brief repetitive condenser shocks of moderate intensity leads, after a latency of less than 0.1 second, to an abrupt increase in activity of sympathetic nerves to the heart and blood ves-

sels. This activity ceases equally abruptly when stimulation is stopped, and for a variable period thereafter all spontaneous activity in these nerves is inhibited. There is no evidence under the conditions of our experiments that any sympathetic after discharge results from hypothalamic stimulation. Blood pressure begins to rise one to two seconds after the start of hypothalamic stimulation and may continue to rise and remain elevated several seconds after stimulation is stopped. The delay in the rise of blood pressure and the prolongation of the rise result from latency and inertia of the sympathetic effector, not from any corresponding delay or persistence of neural activity.

An increase in intensity or frequency of hypothalamic stimulation increases the magnitude and duration of the rise in blood pressure. This increased effector response is brought about by an increase in the number of sympathetic motor neurones set into activity and by an increase in the frequency of response of each neurone.

Multiple pathways descend from both sides of the hypothalamus to make connection with each sympathetic motor neurone. The frequency of response of the neurone is a function of the number of these pathways excited and of the frequency at which they are excited.

While stimulation of the lateral and posterior portions of the hypothalamus yields responses of greater magnitude, no qualitative differences have been noted on stimulation of the preoptic, tuberal, or mammillary divisions.

The buffer reflexes which control the spontaneous sympathetic outflow from the medullary centers also moderate the outflow induced by hypothalamic stimulation. Activation of the buffer afferents may inhibit all response of sympathetic motor neurones to hypothalamic stimulation or reduce the number of these neurones responding. Similarly the frequency of response of any single neurone may be reduced or the response entirely abolished by activation of the buffer afferents. The buffer afferents impress a pulse modulation upon mild increases of sympathetic activity which result from hypothalamic stimulation in exactly the same way that they modulate spontaneous sympathetic outflow. These facts are interpreted as indicating that sympathetic responses from hypothalamic stimulation are mediated through medullary sympathetic centers, not by direct connection of descending hypothalamic pathways with sympathetic motor neurones.

The frequency of firing of a sympathetic motor neurone in response to hypothalamic stimulation is determined by the level of excitation maintained by the hypothalamic volleys, the time course of the recovery cycle, and the degree of activity of inhibitory afferents at some critical point between hypothalamus and motor neurone.

AUTHORS.

Brace, D. E., Scherf, D., and Spire, L. J.: The Effect of Cyclopropane on the Blood Pressure, Stroke-Volume, and Heart Size of the Dog. Anesthesiology 2: 261, 1941.

The blood pressure and cardiac plethysmograms were registered in dogs during and immediately after the administration of cyclopropane for 4.5 to five minutes.

The blood pressure showed a very slight initial rise and then a slow fall lasting about two minutes. During the third and fourth minutes the blood pressure began to rise, and it continued to rise for a few minutes after the anesthesia was stopped. Then it fell gradually to its original level. After the anesthesia was discontinued for twenty seconds, a steep rise in the pressure was followed by a fall of ten seconds' duration in 50 per cent of the experiments.

The amplitude of the pulse waves in the blood pressure tracings diminished during the administration of cyclopropane and rose soon after it had been stopped.

During the administration of the drug, the plethysmogram showed that a marked dilation of the heart occurred in diastole and a less marked dilation in systole. Although the output increased, slight stasis occurred in the heart. About twenty seconds after the administration of cyclopropane was stopped, systole became more forcible and the cardiac volume smaller in systole and diastole. The changes during the systolic phase were more rapid. The stroke volume increased markedly.

Arrhythmias were never observed. Cardiac alternans appeared frequently.

AUTHORS.

Wearn, Joseph T.: Observations on the Morphology and Functions of Some of the Components of the Coronary Circuit. William Sidney Thayer and Susan Read Thayer Lectures. Bull. Johns Hopkins Hosp. **68**: 353, 1941.

Factors influencing the volume and distribution of coronary blood flow are as yet imperfectly understood. Krogh has demonstrated the intermittence of blood flow in the smaller vessels in skeletal muscle. Richards and Schmidt observed an intermittence of flow in the frog's glomeruli, and Bordley, Grow, and Sherman have observed an intermittent flow in the capillaries of the skin. Pulmonary vessels behave similarly. In our laboratory during the past ten years numerous attempts have been made to get evidence of intermittent flow in the heart. To date, however, the evidence from injection experiments in living hearts indicates that the heart utilizes all of its capillaries at all times. The slowly beating heart and the rapidly driven heart under increased load, when injected with a dye, usually show a complete injection of all available capillaries. These experiments, which are still in progress, are by no means final, but the results so far suggest that intermittence of flow does not occur in the coronary circuit.

AUTHOR.

Wearn, Joseph T.: Alterations in the Heart Accompanying Growth and Hypertrophy. William Sidney Thayer and Susan Read Thayer Lectures. Bull. Johns Hopkins Hosp. **68**: 363, 1941.

The changes occurring in hypertrophy increase the distance over which oxygen and metabolites must travel, and in the absence of any obvious compensatory mechanism, such as an increase in the myoglobin content, or an increase in the percentage saturation of oxygen in the coronary venous blood, one might raise the question as to whether hypertrophy is an actual hindrance to the efficiency of the heart. Whether a compensatory increase in the volume of blood flow in the coronary circuit occurs with hypertrophy is unknown.

AUTHOR.

Dally, J. F. Halls: Life and Times of Jean Nicholas Corvisart. Proc. Roy. Soc. Med. **34**: 239, 1941.

This historic biographic sketch of Corvisart in medieval medicine describes his contributions to the development of the modern study of cardiology.

MCCULLOCH.

Schecter, A. E., Wiesel, B. H., and Cohn, C.: Peripheral Circulatory Failure in Diabetic Acidosis and Its Relation to Treatment. Am. J. M. Sc. **202**: 364, 1941.

Eight patients with diabetic acidosis were studied. Initially elevated hemoglobin, hematocrit and serum protein with a decrease following administration of fluids showed the presence of dehydration and hemoconcentration. Peripheral blood flow

in the hand, as measured by the plethysmograph, was reduced. Venous oxygen saturation was high in the presence of marked reductions in peripheral blood flow. Physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis. The existence of an unusually high venous oxygen saturation in the presence of a reduced peripheral blood flow suggests a failure of oxygen utilization by the tissues. Possible causes suggested for the failure of oxygen utilization are (1) inability to utilize carbohydrate; (2) ketosis, or (3) acidosis. These findings point out the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

The importance of the prompt restoration of blood volume and the maintenance of adequate circulation in the treatment of diabetic acidosis is stressed.

AUTHORS.

Cos, A. J., Jr., and Dock, W.: The Capacity of the Renal Vascular Bed in Hypertension. J. Exper. Med. **74**: 167, 1941.

By using kerosene and avoiding post-mortem rigor, one can obtain perfusion rates in kidneys nearly five times faster than those reported by observers who perfused kidneys immediately post mortem with saline solution, only half as viscous as kerosene.

The results obtained by kerosene perfusion indicate possible renal blood flow 50 to 100 per cent greater than that measured by Smith and his co-workers in living men by diodrast clearance under normal conditions, and about as high as those observed in febrile subjects. Like the diodrast method, kerosene perfusion shows a striking decrease in renal vascular bed between early maturity (age 18 to 35) and senescence (45 to 60). This decrease is about 25 per cent.

Most kidneys from patients with hypertension without uremia have vascular beds in the normal range, but a few show great decreases in capacity for blood flow. This evidence is interpreted as another indication that renal arteriosclerosis is often a result, rarely a cause of hypertension. Significant occlusion of large renal arteries is rare.

Uremia due to amyloid may occur with no significant decrease in renal vascular bed, but the uremia of renal sclerosis, glomerulo- or pyelonephritis is associated with reduction of vascular bed to very low levels.

AUTHORS.

Dock, W.: The Capacity of the Coronary Bed in Cardiac Hypertrophy. J. Exper. Med. **74**: 177, 1941.

After the elimination of vascular rigor, perfusing human hearts with kerosene under pressure post mortem gives values for coronary flow which seem to be an index of the maximum possible flow during life. This is 3.1 c.c. per gram per minute at 100 mm. Hg in normal men under 40. It is 35 per cent lower in the hearts of those 60 to 80 years old and also falls in hypertrophied hearts. In old people it is 30 per cent lower in hearts over 600 Gm. than in those under 350; in patients 40 to 60 years old it is 37 per cent less in hearts over 600 as compared with those under 350 Gm.

In discussion it is brought out that, while the decrease in coronary capacity associated with age or hypertrophy may play a part in predisposing some hearts to congestive failure, there is no evidence that the hypertrophied heart has an inadequate oxygen supply or that its fibers are too thick for adequate oxygen diffusion. Congestive failure cannot be ascribed to anoxia except in the presence of severe anemia, coronary occlusion, or tachycardia with low blood pressure. Decrease in

perfusibility with age and growth may be a perfectly normal adaptation to the needs of the tissue; the perfusibility of the heart of the young adult is about half that of an infant of 2 years.

AUTHOR.

Wolf, S., and Hardy, J. D.: Studies on Pain. Observations on Pain Due to Local Cooling and on Factors Involved in the "Cold Pressor" Effect. J. Clin. Investigation **20:** 521, 1941.

Pain due to local cooling is altogether separate from the sensation of cold itself. It is apparently mediated through small, nonmyelinated fibers of class C. Its intensity, however, depends directly upon the degree of cooling. The stimulus required for the production of "cold pain" may be found in the thermal gradient in the tissues of the immersed hand. It is possible that this stimulus brings about a painful vasospasm in the part. Relaxation of this local vasospasm may occur as the thermal gradient is decreased, thus accounting for "adaptation." It appears that the "cold pressor" effect is a measure of reaction to pain.

AUTHORS.

Abramson, D. I., and Fierst, S. M.: The Peripheral Vascular Response to Exercise in the Hyperthyroid State. J. Clin. Investigation **20:** 517, 1941.

The post-exercise blood flow repayment was generally found to be much greater in the hyperthyroid state than in the period following subtotal thyroidectomy.

A correlation was apparent between the level of oxygen consumption and the magnitude of the excess blood flow elicited by the exercise.

Exercise places a much greater load upon the circulation in hyperthyroidism than in the normal state.

AUTHORS.

Dressler, M., and Moskowitz, S. N.: Fetal Electrocardiography and Stethography. Am. J. Obst. & Gynec. **41:** 775, 1941.

Forty gravidas were studied routinely in the last two months of pregnancy to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases, the fetal electrocardiogram in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of fetal heart sounds depends upon the site at which the microphone is applied, and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive, a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R wave of the fetal electrocardigram.

The factors involved in negative electrocardiograms are a nervous mother, a small fetus, maternal tachycardia, and possibly fetal sinus arrhythmia.

The combined tracings give permanent records of documental value. The maternal electrocardiogram is also recorded.

The use of fetal electrocardiography and fetal stethography for routine and consultation purposes is recommended because of the simple procedure involved and the ease with which tracings can be interpreted.

A case of breech presentation with positive tracing in Lead I, and variations in maternal and fetal rate is discussed.

AUTHORS.

Hoff, H. E., Nahum, L. H., and Kaufman, W.: The Nature of Leads I and III of the Electrocardiogram. Am. J. Physiol. **134**: 390, 1941.

Lead I records the algebraic summation of the anterior levocardiogram and the posterior dextrocardiogram.

Lead III records the algebraic summation of the anterior dextrocardiogram and the posterior levocardiogram.

AUTHORS.

Nahum, L. H., Hoff, H. E., and Kaufman, W.: Formation of the R Complex of the Electrocardiogram. Am. J. Physiol. **134**: 384, 1941.

The R complex of the electrocardiogram results from the algebraic summation of the initial portions of the dextro- and levocardiograms.

When the R complex is upright, its initial deflection is the upstroke of the dextrocardiogram, while the downstroke is produced by the onset and development of the levocardiogram.

When the R complex is directed downward, the downstroke is the initial portion of the levocardiogram, while the upstroke is produced by the onset and development of the dextrocardiogram.

The amplitude of the R complex varies with the interval separating onset of the dextro- and levocardiograms. The maximum amplitude is limited by the amplitude of the component dextro- or levocardiograms.

AUTHORS.

Taquini, Alberto C.: The Electrocardiogram in Experimental Chagas Disease. Rev. argent. de cardiol. **8**: 115, 1941.

Inoculation of puppies with *Tripanozoma Cruzii* is followed by marked electrocardiographic alterations—arrhythmias and changes in auricular and ventricular complexes, evidence of myocardial damage.

AUTHOR.

Steele, J.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of Three Cases. J. Clin. Investigation **20**: 473, 1941.

Review of the knowledge of levels of arterial pressure in 217 cases of coarctation of the aorta makes untenable the assumption that increase in peripheral resistance is situated in the upper half of the body only.

In two of three cases of coarctation of the aorta, diastolic pressure has been shown by intra-arterial measurement to be elevated above 100 mm. Hg in the femoral as well as in the radial arteries. This is interpreted as evidence of general increase in arteriolar tone throughout the body.

In so far as the distribution of peripheral arteriolar resistance is concerned, arterial hypertension in coarctation of the aorta does not differ from the common forms of arterial hypertension.

AUTHOR.

Liebow, A. A., and McFarland, W.: "Corrected Transposition," and Persistent Rudimentary "Right Aorta" as Evidence in Support of Spitzer's Theory. Arch. Path. **32**: 356, 1941.

In this study Spitzer's theory has received confirmation (1) in the analysis of a very complex anomaly, bulboventricular inversion with transposition of the great vessels, and (2) in suggestive direct evidence of the existence of a homologue of the reptilian right aorta, which is recorded for the first time as observed in an anomalous human heart.

AUTHORS.

Hahn, P.: Reflections on the Mechanism of Spontaneous Rupture of the Heart. Cardiologia **5**: 33, 1941.

In a case of mitral disease, which developed over several years and ended with massive pulmonary embolism, a rupture of the endo- and myocardium in the vicinity of the right auricle was found. Blood had infiltrated into the subepicardial tissue.

The histologic examination of the site of the rupture revealed no prior lesion that could have explained the tear: the in toto definitely hypertrophic wall of the ventricle showed decreased thickness of the myocardium between the trabicles; the fibers of the myocardium were, however, unchanged. Microscopic examination of other parts of the heart revealed no damage.

Apart from mitral stenosis (without fresh inflammatory changes) and hypertrophy, the heart was in good condition. This permits the assumption that the overpressure in the ventricle caused by the pulmonary embolism was responsible for the rupture.

After consideration of the physical and hemodynamic appearances, an attempt was made to account for the potentials concerned in the genesis of the rupture.

This consideration showed the complexity of these laws and the experimental difficulties to be overcome in order to clear up the problem. With regard to the right of the heart the data so far at our disposal are very incomplete; all former experiments had reference to large circulation, which is more amenable to research.

AUTHOR.

Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients With Antecedent Shock. Arch. Int. Med. **68**: 181, 1941.

In a series of 350 cases, eleven were found in which the heart showed multiple fresh coronary arterial occlusions, all occurring in the presence of shock. Of these, eight were instances of multiple thrombosis and three were instances of multiple fresh nonthrombotic occlusions. The shock was due to conditions other than myocardial infarction in eight of these eleven cases. In all, the patients were elderly and gave marked clinical and pathologic evidence of coronary disease. In addition, a single fresh coronary occlusion was found in thirty-eight cases, in twenty-two of which it was due to a thrombotic and in sixteen to a nonthrombotic mechanism. Shock due to noncardiac causes or congestive failure was present in approximately half of these cases.

Shock, no matter how produced, may lead in elderly patients, particularly in those showing evidence of coronary arteriosclerosis, to the development not only of single, but often of multiple, fresh coronary arterial occlusions. To avert such disastrous complications, the manifestations of shock, such as lowering of blood pressure, tachycardia, and dehydration, must be combated with particular vigor in these patients.

AUTHOR.

Simburg, E. J.: Spontaneous Cardiac Rupture. Canad. M. A. J. 45: 112, 1941.

Two cases of spontaneous cardiac rupture are reported from our own service. The clinical and pathologic findings agree essentially with those of several larger investigations. The latter are discussed in some detail.

AUTHOR.

Jason, R. S.: Insufficiency of the Aortic Valve Due to Syphilis: A Study of Its Genesis. Arch. Path. 32: 409, 1941.

The syphilitic distortions of the aortic valve and ring generally accepted as the causes of insufficiency and the usual explanations of their genesis are described and discussed briefly.

The study of a series of twenty-seven syphilitic hearts, including gradations from chronic to fulminating lesions, disclosed aortic valve distortions falling outside of those commonly described, which could not be accounted for by the generally accepted explanations of pathogenesis.

All of the valve distortions studied appeared to have been due to two processes: (a) a destructive inflammation of the aortic wall resulting in destruction and dislodgment of the cusp attachments at the commissures and (b) a reparative fibrosis.

These two processes, destructive inflammation and reparative fibrosis, are set forth and discussed as the basic factors in the genesis of aortic insufficiency due to syphilis. Reference is made to earlier brief statements to this effect by Mallory and Norris.

Support for the idea that destruction of tissue plays a significant part in the production of syphilitic valvular distortions is found in the partial reproduction of such distortions by dissection of normal valves.

AUTHOR.

Prado, A. De A.: Intrapericardial Aortic Aneurysm. Rev. argent. de cardiol. 8: 105, 1941.

A case is reported of intrapericardial aortic aneurysm confirmed by autopsy; during life it presented a difficult problem of differential diagnosis from a diverticulum of the pericardium.

The great size of the paracardiac tumor, its faint pulsation, the angulated form of the radiological contour, and the long course of the malady may be found in both cases. Synchronism of the tumor pulsations with those of the aortic arch as shown by roentgenkymograms may be a sign of aneurysm of diagnostic value.

In cases of highly located intrapericardial aortic aneurysms, as the case reported, there is no typical syndrome which may distinguish them from extrapericardial aortic aneurysms, as Cossio and others hold. On the contrary, those of low, supravalvular location, one case of which is briefly reported, have a typical syndrome.

AUTHOR.

Bohnengel, C.: Auriculo-Ventricular Heart Block With Stokes-Adams' Syndrome in a Patient With Syphilitic Heart Disease and Diffuse Myocarditis. J. Indiana M. A. 33: 617, 1940.

A case presenting clinical and post-mortem evidence of syphilitic heart disease with aortic insufficiency, cardiac enlargement, and congestive heart failure is reported. The illness was complicated by auriculoventricular heart block and Stokes-Adams' attacks. The patient died during an attack, and at autopsy a diffuse myocarditis was found in the interventricular septum. The combined clinical, laboratory, and au-

topsy findings point to syphilis as a possible etiologic agent for the production of the lesion and its accompanying disturbance in conduction, but conclusive proof is lacking.

AUTHOR.

Carr, F. B.: Heart Disease in Pregnancy. M. Ann. District of Columbia **10**: 1, 1941.

In the first years following the establishment of the Prenatal Cardiac Clinic at the Boston Lying-In Hospital, there was a mortality rate of about 12 per cent among pregnant cardiac patients. This rate gradually fell, and in 1933 it was about 6.4 per cent; at the present time less than 3 per cent of all cardiac patients succumb to the dangers of pregnancy. It has been the experience at this hospital and also at the Worcester City Hospital, where a similar clinic has been existent for about ten years, that nearly half of this expressed mortality occurs in patients who have not attended the clinic but have been hastily referred to the hospital with the sudden onset of critical heart failure.

It is possible that with adequate prenatal care, which implies frequent and careful observation of the patient by the internist and the obstetrician, as well as implicit cooperation on the part of the patient, the mortality rate among pregnant cardiac patients might be gradually lowered, to finally approximate the fatality rate in everyday obstetrics. However, there are several barriers that appear insuperable now, such as subacute bacterial endocarditis, accounting for 0.8 per cent mortality, and fatal embolism, also accounting for 0.8 per cent. It is wishful thinking to believe the cardiac patient can be as good a risk as the normal woman. The astonishing and gratifying feature is how high a percentage of them can bear children and apparently be none the worse for it.

AUTHOR.

Browning, J. S., and Clark, C. J.: Paroxysmal Auricular Tachycardia Complicating Pregnancy. J. Indiana M. A. **34**: 21, 1941.

Two cases of paroxysmal auricular tachycardia complicating pregnancy are reported.

The incidence of this condition in pregnancy is rare, occurring in less than 1 per cent of known cardiac patients and much less in otherwise normal persons. The history of previous attacks should warn of recurrence during pregnancy.

Paroxysmal auricular tachycardia usually occurs in otherwise normal hearts.

Quinidine is an effective drug in stopping attacks of paroxysmal auricular tachycardia and may be used in pregnancy without fear of precipitating premature labor.

Electrocardiographic evidence of myocardial damage is often unreliable, because it may represent merely cardiac fatigue.

AUTHORS.

Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: II. The Association of Hypertension With Organic Renal Disease. Arch. Int. Med. **68**: 261, 1941.

Two hundred fifty cases of so-called essential hypertension have been studied with a view to ascertaining the presence of organic renal disease. One hundred seventy-eight have been studied especially as regards the genitourinary tract. Evidence of renal disease of a nature not usually considered to be dependent on hypertension has been found in 113 cases.

Organic renal disease is a common occurrence in cases of essential hypertension. Examination of the genitourinary tract for abnormalities is an important part of the study of cases of hypertension. A history of renal disease often antedates the onset of arterial hypertension, even when no abnormality can be found. There is justification for regarding the condition in these cases no longer as "essential" hypertension but a different disease.

AUTHORS.

Corcoran, A. C., and Page, I. H.: Renal Aspects of Experimental and Clinical Hypertension. J. Lab. & Clin. Med. **26**: 1713, 1941.

This is a critical review of the recent publication describing the relationship between the changes in the kidney and hypertension. It is stated that the final origin of hypertension remains obscure, for the demonstration of the part played by the renal pressor system clarifies some aspects of its etiology but, at the same time, poses new problems.

MCCULLOCH.

Lamport, H.: Formulae for Afferent and Efferent Arteriolar Resistance in the Human Kidney: An Application to the Effects of Spinal Anesthesia. J. Clin. Investigation **20**: 535, 1941.

The application of Poiseuille's law to the kidney has been discussed, and formulas have been developed to measure clinically, in man, afferent and efferent arteriolar resistance. A practical application to available clinical data on the renal effect of spinal anesthesia (denervation) in normal man has also been offered. At present, while normal man may lack tonic central nervous control of renal blood flow, this does not appear to have been demonstrated. The evidence also does not preclude autonomous control by the kidney of its blood supply.

Incidentally, empirical formulas for the viscosity of human plasma and whole blood have been derived from observations in the literature.

AUTHOR.

Lamport, H.: The Relative Changes in Afferent and Efferent Arteriolar Resistance in the Normal Human Kidney. J. Clin. Investigation **20**: 545, 1941.

Formulas for the afferent and efferent arteriolar resistance to renal blood flow in man have been applied to available data for normal subjects under ischemic, basal, and hyperemic renal conditions.

It has been found that the resistance of both sets of arterioles vary simultaneously in maintaining constant glomerular filtration in the basal state and in ischemia and pyrogenic hyperemia of the human kidney.

At the mean basal state, a 1 per cent decrease in renal blood flow per unit diodrast tubular mass is caused by approximately a 0.2 per cent decrease in afferent arteriolar resistance and a 0.9 per cent increase in efferent arteriolar resistance.

The heat loss due to friction of the blood flowing through the efferent arterioles is not approximately constant.

AUTHOR.

Corcoran, A. C., Smith, H. W., and Page, I. H.: The Removal of Diodrast From Blood by the Dog's Explanted Kidney. Am. J. Physiol. **134**: 333, 1941.

Diodrast intravenously infused in dogs is unequally distributed between the plasma and red blood cells, the distribution ratio between cell and plasma water being approximately 0.50.

At low renal loads the extraction of diodrast from arterial plasma during its passage through the explanted kidneys of dogs averaged 0.84. Diodrast extraction was not affected by uninephrectomy.

Renal extraction of diodrast from arterial red blood cells averaged 0.20.

The removal of diodrast from arterial blood by the dog's explanted kidney is such that at low renal loads the ratio $\frac{\text{plasma diodrast clearance}}{\text{renal plasma flow}}$ is approximately 0.87.

AUTHORS.

Friedman, B., Jarman, J., and Klemperer, P.: Sustained Hypertension Following Experimental Unilateral Renal Injuries. Effects of Nephrectomy. Am. J. Med. Sc. **202:** 20, 1941.

Sustained hypertension was produced in rats by means of unilateral renal injury (perinephritis from enveloping the kidney in a cellophane envelope).

Hyalinized and necrotic vascular lesions were observed in some animals. Their presence was associated with rapidly rising severe hypertension but was not related to the duration of hypertension or to the presence of nitrogen retention.

Removal of the injured kidney from the hypertensive animals resulted in a decline in blood pressure, not to the prehypertensive level, but to some point above it depending upon the severity of the hypertension. Maintenance of an elevated pressure long after removal of the injured kidney suggests that irreversible changes have occurred which may or may not be related to the changes in the vessels.

AUTHORS.

Jeffers, W. A., Montgomery, H., and Burton, A. C.: Types of Orthostatic Hypotension and Their Treatment. Am. J. M. Sc. **202:** 1, 1941.

The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

The physiologic importance of peripheral vasomotor activity, plus changes in heart rate, is emphasized.

A clinical study of normal subjects, patients following sympathectomy, and those with orthostatic hypotension is reported, using chiefly the following criteria: blood pressure, pulse rate, digital blood flow, and skin temperature.

According to their reactions to the tests above, our patients have been classified as having orthostatic hypotension due to slight, or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

These patients showed orthostatic hypotension in association with: lesions of the central and peripheral nervous systems (communicating hydrocephalus, tabes dorsalis, and nerve injury secondary to arterial occlusion), the post-infectional state, and venous angioma. In one patient no etiology could be discovered.

The clinical evaluation of patients with orthostatic hypotension is discussed and a rationale of treatment is outlined.

AUTHORS.

Galdston, M., Govons, S., Wortis, S. B., Steele, J. M., and Taylor, H. K.: Thrombosis in the Common, Internal and External Carotid Arteries. Arch. Int. Med. **67:** 1162, 1941.

The case histories of two patients with right hemiplegia and mixed aphasia associated with thrombosis of the carotid arteries of the left side and sensitivity of the carotid sinus reflex of the other side are presented. The literature dealing with thrombosis of the carotid arteries is summarized.

Thrombosis of the carotid vessels was suspected because of the absence of arterial pulsations. The diagnosis was confirmed by study of cerebral arteriograms and encephalograms, surgical exploration and gross and microscopic examination of the specimens.

Careful examination of the arteries of the neck in all patients with hemiplegia, convulsive seizures, or syncope may lead to more frequent diagnosis of thrombosis of the carotid arteries. Often arteriography can be a diagnostic aid.

AUTHORS.

Sappington, S. W., and Horneff, J. A.: Tibial Artery Changes in Comparison With Those of the Radial and Coronary Arteries. Am. J. Med. Sc. **201**: 862, 1941.

Tibial artery age period changes and arteriosclerotic changes short of occlusive lesions consist of the development of a progressively thickening intimal collar of split elastica and longitudinally arranged interwoven connective tissue, together with more frequent and more voluminous medial calcification. These changes are similar to those found in the radials, but are slightly greater for the intima and decidedly greater for the media. Medial calcification was about three times more common in the tibial than in the radial in this series. Atherosclerosis is seldom a feature of tibial artery change. Altogether the intimal thickening in the tibial as well as the radial is slight, especially as compared with the coronary, and seldom threatens the integrity of the lumen. As in the radial, the anatomic condition of the tibial artery has no inferential bearing on coronary sclerosis.

AUTHORS.

Deutsch, F., Ehrentheil, O., and Peirson, O.: Capillary Studies in Raynaud's Disease. J. Lab. & Clin. Med. **26**: 1729, 1941.

In this investigation the capillary response was studied in twenty-nine cases of Raynaud's disease.

1. Capillaroscopic observation of cases of Raynaud's disease shows that the disease may be present before the appearance of the clinical symptoms. In these cases abnormal capillaries can be seen when other vasomotor symptoms are not present.

2. In the majority of cases of Raynaud's disease there exists a persistence of the subpapillary plexus and a persistent connection between it and the outgrowing capillaries.

3. Two objective measurements are introduced to test the dynamics of capillary circulation: (a) reflux time, i.e., that time which elapses before the capillary flow ceases, when the upper arm is compressed with a blood pressure cuff, pumped up to 30 mm. above the systolic blood pressure; (b) critical capillary pressure, i.e., that pressure at which the flow once again reappears when the cuff in the above experiment is gradually decompressed at the rate of 10 mm. per two seconds.

4. Capillaroscopy can define the severity of the disease more accurately than the gross clinical findings.

5. The preganglionic sympathectomy has a distinct influence on the capillary picture of Raynaud's disease: (a) in twelve of fourteen cases the speed of the blood flow increased; (b) in cases with a slow reflux time, the time increased, and vice versa; (c) in ten of fifteen cases the width of the capillaries decreased; (d) the capillary permeability decreased; (e) the dilatation of the excretory ducts of the sweat glands vanished after operation; (f) these changes in the capillary picture after sympathectomy become less distinct in time; (g) the subjective symptoms of the patient are to some extent independent of the clinical picture. Some have the

same typical capillary picture as before operation, even though relieved of complaints. Others show objective improvement clinically, but retain their subjective complaints, because a neurosis may become apparent, which may have been a part of the picture from the beginning.

AUTHORS.

Crouch, J. H.: Glomus Tumours: Clinical Picture and Physiology. Canad. M. A. J. **44**: 356, 1941.

Certain interrelationships which exist between glomus tumors and the sympathetic nervous system are discussed briefly. They are especially evident in the symptoms of pain and sweating. It is believed that the neurological features are more important than the vascular ones.

AUTHOR.

Plewes, Burns: Multiple Glomus Tumours: Four in One Finger Tip. Canad. M. A. J. **44**: 364, 1941.

A case of multiple glomus tumors on the finger is reported. There is no evidence that the multiplicity of tumors gives rise to any peculiarly different or more severe symptoms. It is suggested that the rare case of recurrence may have been of multiple glomus tumors, the secondary tumors being very small at the time of the first operation.

MCCULLOCH.

Hertzman, A. B.: The Relative Responses of the Dorsal Metacarpal, Digital, and Terminal Skin Arteries of the Hand in Vasoconstrictor Reflexes. Am. J. Physiol. **134**: 59, 1941.

The participation of the intermediate hand arteries, the dorsal metacarpal arteries, and the digital arteries, in the vasoconstrictor reflexes of the hand, has been studied by recording their volume pulses with the photoelectric plethysmograph.

These arteries do not usually participate in the so-called spontaneous waves (Figs. 1, 2, 6, and 7) or in the vasoconstrictor reflexes elicited by loud noises (Figs. 3 and 8), by immersion of opposite hand in ice water (Fig. 4), or by application of cold to the finger whose pad pulses are being recorded (Figs. 5 and 9).

These results are most simply explained by considering the vasomotor reflexes as highly selective with respect to the vascular topography involved in the reactions.

AUTHOR.

Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg: Its Clinical Significance as Exemplified in Three Hundred and Fifty-one Autopsies. Arch. Int. Med. **68**: 1, 1941.

Thrombosis of the deep veins of the leg is appallingly frequent among middle-aged and older persons forced to bed for varying periods of time. The incidence in the present study was 52.7 per cent.

Bilateral involvement was found 110 times, and unilateral, seventy-five times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius.

Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good authority for the belief that, although

fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet. From the standpoint of prophylaxis and treatment, recognition of this is most important.

Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries. Repeated embolic episodes are more frequent than a single massive attack. Multiple small fragments can also do harm by placing an added burden on an already embarrassed circulatory system.

In the present series there was little difference in the incidence of thrombosis between medical and surgical patients or between males and females.

Phlebitis, either as a cause or as a complication of thrombosis, had a minor role in our cases.

As a rule, phlebothrombosis of the deep veins of the leg is clinically silent and for this reason is likely to be forgotten until embolic phenomena appear.

We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of active exercise or the aid of gravity in the maintenance of an efficient venous circulation.

Planned and supervised voluntary movement and the elimination of too much comfort for the legs should do much to reduce incidence of thrombosis and its all too frequent sequel—pulmonary embolism.

AUTHORS.

McDowall, R. J. S.: Problems of Circulation. The Oliver-Sharpey Lectures to the Royal College of Physicians of London. Brit. M. J. 2: 39, 75, 1941.

A biographical sketch of George Oliver describing the state of physiology of the circulation in his time and the part played by Oliver in laying down foundations for further development of this science is presented. Oliver worked for a closer relationship between physiology and medicine.

McCULLOCH.

Turner, G. G.: A Bullet in the Heart for Twenty-Three Years. Surgery 9: 832, 1941.

The case of a man who is still alive and well and who has been going about his daily work for the last twenty-three years with a machine gun bullet lodged in the wall of the left ventricle is reported. It was possible to remove this foreign body at operation.

McCULLOCH.

Reynolds, Samuel R. M.: Dermovascular Action of Estrogen, The Ovarian Follicular Hormone. J. Invest. Dermat. 4: 7, 1941.

A review is given of the experiments reported in earlier papers on the vasodilating effect of estrogen on the capillaries and venules in the skin of the ear of the rabbit and in the human male. The increase in finger-volume involves the capillaries and venules, and does not alter appreciably the rate of blood flow through the skin. The response is in the same direction, though less than that seen in the genital tract following injection of estrogen.

A summary is made of work now in progress on the dermovascular effect of estrogen in women in menopause. It is shown that two types of response may occur, one, a sustained plateau, the other, a flush-type of response. The latter is observed in women who are nervous before treatment, or during a period of return

of symptoms in the course of treatment. The dermovascular effect of estrogen appears to become less marked as relief from vasomotor disturbances takes place.

Comparison is made of the menopausal flush and the dermovascular reaction to estrogen. It is shown that in both vasodilatation occurs, but that in the menopausal flush the effect is in part due to arteriolar dilatation, and in the estrogen response, the smallest vessels beyond the arterioles are concerned. The former involves intermediation of nervous activity (inhibition of arteriolar tone), the latter appears to be a direct effect of the hormone on tissues in or about the blood vessels.

AUTHOR.

Rubin, M. I., and Rapoport, M.: The Mode of Action of Magnesium Sulphate in Reducing the Hypertension of Acute Glomerulonephritis. Am. J. M. Sc. **201**: 734, 1941.

In the patient with acute glomerulonephritis and hypertension, magnesium sulphate lowers the blood pressure without producing dehydration.

The intravenous administration of hypertonic sucrose produces diuresis, and generalized and cerebral dehydration, without lowering the blood pressure. Occasionally it elevates the blood pressure. The dangers of this secondary rise in blood pressure in the acute nephritic are pointed out.

Magnesium sulphate in the doses employed may be ineffectual in patients with large urinary volumes.

The mechanism by which magnesium sulphate reduces elevated blood pressure is discussed.

AUTHORS.

LeRoy, George V.: The Effectiveness of the Xanthine Drugs in the Treatment of Angina Pectoris. I. Aminophylline. J. A. M. A. **116**: 921, 1941.

Sixty-eight patients with angina pectoris were given aminophylline or placebos in varying amounts over a period of two years. In general, aminophylline benefited 75 per cent of the sufferers. Placebos and sedative drugs were reported beneficial by about 20 per cent of the group. When patients who had been benefited by the use of aminophylline were given placebos or stopped taking the drug, about 80 per cent experienced a return of symptoms within less than three months.

AUTHOR.

Book Reviews

La Insuficiencia Cardiaca: By Dr. Cristián Cortés Lladó, Antiguo Jefe del Servicio de Cardiología de Cataluña. De la Escuela de Medicina de Barcelona. Compañia General Editora, S. A., Mexico, D. F., 1940, 186 pages, 30 illustrations, $3.00.

This booklet, which was designed for general practitioners, deals with the general problem of congestive heart failure. It follows the classical pattern of the French School, from Beau to Vaquez, from Lian to Laubry.

The conception of isolated failure of either ventricle, and of the left auricle, is accepted.

In a few short chapters the author describes the contributions that radiology, electrocardiography, and measurement of cardiac output have made to the diagnosis of heart failure. In spite of the many interesting details, the conclusions reached in these chapters are not always convincing.

A large bibliography is included. However, there is no mention of many studies on heart failure which have been published in the last ten years, notably those of Luisada, Rigoni, Harrison, Fishberg, and Altschule. If these studies had been taken into account, some of the conclusions might have been modified.

In general, the book is evidence of the difficulty of writing for general practitioners a brief, but complete and modern, description of heart failure.

Aldo Luisada.

Influence of the Thyroid Hormone on Heart and Circulation: By Hâkon Rasmussen, Institute of Physiology, University of Oslo. Acta med. Scandinav., Suppl. CXV, 1941; 202 pages, 12 figures, and 38 charts.

After an excellent review of the literature, this monograph is concerned with the author's prolonged investigations on twenty trained dogs, of which twelve were fed thyroid, three were given thyroxine, and five received dinitrocresol over a period of many months, unless interrupted by death.

Most of the animals which received thyroid or thyroxine did not seem unusually nervous, although all showed a marked increase in oxygen consumption. Tachycardia was regularly present early in the experiments, but, in the majority of instances, the heart rate later declined to a normal level, with intervals of tachycardia. Exercise tests resulted in abnormal tachycardia, so that instability of the heart rate, rather than constant tachycardia, was characteristic.

The systolic pressure rose, but the diastolic was little affected. The cardiac output (Fick method) was increased pari passu with the oxygen consumption, so that the average arteriovenous difference was unaltered. The electrocardiogram exhibited characteristic, but often temporary, changes; inversion of the T waves and an increase in the Q-T interval were the most constant alterations.

The dogs died in a state of circulatory insufficiency, ushered in by extreme tachycardia, with low cardiac output and diminishing blood pressure, but without congestive phenomena. The autopsies showed no characteristic changes in the heart or vessels which might explain either death or the circulatory effects; adrenal hypertrophy was the most constant abnormality.

Feeding vitamin B_1, in addition to thyroid, did not ameliorate the effects of the latter.

Dogs which were fed dinitro-v-cresol developed increases in oxygen consumption comparable to those in the thyroid group, but, in contrast, had fever and bradycardia.

The author concludes that the thyroid hormone has a primary, deleterious effect on the heart and circulation and that the final circulatory failure is not secondary to the increased cardiac work. The tachycardia, far from being a compensatory mechanism, is extremely detrimental.

This is the most extensive study of the effects of experimental hyperthyroidism on the circulation that has been reported. The material is well arranged, and the prose is clear. The author is interested in throwing light on human hyperthyroidism by the method of animal experiments, so that clinicians will find the monograph readable and interesting. Most of the results corroborate the view of the disease which is current in this country. The monograph is well up to the high standard which we have been led to expect from Scandinavian research.

ISAAC STARR.

CARDIAC CLASSICS. A COLLECTION OF CLASSIC WORKS ON THE HEART AND CIRCULATION, WITH COMPREHENSIVE BIBLIOGRAPHIC ACCOUNTS OF THE AUTHORS: By Fredrick A. Willius, M.D., Chief, Section of Cardiology, The Mayo Clinic, and Thomas E. Keys, M.A., Reference Librarian, The Mayo Clinic. The C. V. Mosby Co., St. Louis, 1941, 858 pages, $10.00.

"Cardiac Classics" is introduced by a foreword from the pen of Donald C. Balfour. In his short communication Dr. Balfour writes, "In the appraisal of medical literature, students and practitioners are likely to overlook the writings of those who established the fundamentals upon which subsequent progress has been made. These epoch-making contributions are also evidence of the fact that in the study of disease thorough and accurate observation is the first requirement and supersedes other methods."

The authors have chosen papers quite in keeping with Dr. Balfour's suggestions. These original papers present the work of investigators who carried on research in spite of obstacles, and most of these investigations were hampered by an almost total lack of equipment. As one reads these essays and tries to visualize the effort and persistence necessary to achieve so much, the wonder is not that medical science lagged so long, but that it has achieved so much with resources so slender.

The first paper included in the series is the essay, "On the Motion of the Heart and Blood in Animals," which William Harvey presented in 1628; the last (save a poem by Oliver Wendell Holmes) is the paper by James B. Herrick on "The Clinical Features of Sudden Obstruction of the Coronary Arteries," published in 1912. In between are fascinating contributions. All of these are important in the history of cardiac disease; the progress of investigation in cardiac structure, function, and disease is portrayed in these original papers.

Each contribution is accompanied by a likeness of the author; many of these are copies of portraits. Also, a short biography is the preface to each essay, which adds much to the interest. Thus the reader has a glimpse of the social background, the status, and activities of the leading practitioners through several generations.

Fifty-two communications from fifty-one authors make up the collection. Among many original essays, one finds Malpighi's report "About the Lung," "Early Experiments on Blood Pressure and Blood Velocity," the work of Stephen Hales, Auenbrugger's essay on "Percussion of the Chest," and Withering's "Account of the Foxglove." A long chapter is given to Laennec's "Treatise on Mediate Auscultation." Corvisart, Caleb Parry, James Hope, Corrigan, Stokes, Duroziez, Potain,

Von Leeuwenhoek, Morgagni, Traube, Cohnheim, His, Jr., and many others who shared in the development of the knowledge of cardiac disease are represented in this collection.

The book is not devoted entirely to the pioneers of research who laid the foundations of the knowledge of cardiac disease and developed the facts of cardiac physiology and pathology slowly through two hundred years and more. Important communications of fundamental value of recent date and modern type are included. Einthoven's first presentation of the use of the string galvanometer in the electrocardiograph is included. Among the papers from the modern group are those by James Mackenzie, Walter Keith, and Broadbent. One very interesting lecture is that given in 1896 by Francis H. Williams on the use of the fluoroscope for determining the outline of the heart.

The reviewer agrees with the authors that "it is reasonable to conclude that the classics of medical antiquity form the basis of modern medicine and that the physician of today relinquishes many cultural advantages when he avoids the acquaintance with his distinguished predecessors."

The book is beautifully bound and well printed, and the numerous reproductions of portraits are satisfactory. To the physician who is interested in medical history, particularly if much of his work is with cardiac patients, this book will make an especial appeal; it can be heartily recommended to all physicians who find pleasure and instruction in the study of the achievements of the great men whose vision and industry laid a sure foundation.

JAMES G. CARR.

MANAGEMENT OF THE CARDIAC PATIENT: By William G. Leaman, M.D., Assistant Professor of Medicine in charge of the Department of Cardiology, Women's Medical College of Pennsylvania. The J. B. Lippincott Co., Philadelphia, 1940, 705 pages, 255 illustrations, $6.50.

Those who believe that any book review worthy of the name must consist largely of adverse criticism need waste no time reading this one. To the present reviewer Dr. Leaman's book seems distinguished by many excellent qualities, and easily to be rated among the few good volumes devoted to treatment of the sick patient. It differs considerably from most textbooks on heart disease, as one would expect from its title. The author's aims are set forth clearly in the preface, where he modestly states that "this small volume attempts to assemble the facts that are most essential in the management of the cardiac patient," and he indicates further that it was written primarily for the guidance and help of the general practitioner.

It is not a particularly small volume, even in comparison with the supergigantic books that are the current fashion in medical texts. It contains about 650 pages, not counting eighteen pages of selected bibliography. After reading the entire book carefully, I find it difficult to believe that it could be reduced in size without materially impairing its value.

Emphasis is properly laid chiefly upon the details of treatment, but all modern methods of diagnosis are discussed in detail and their value appraised. Heart disease is classified according to etiology and functional capacity, rather than upon the basis of structural lesions. All the recognized etiologic types (rheumatic, syphilitic, hypertensive, etc.) are adequately considered, and, in addition, there are valuable chapters upon the heart in pregnancy, cardiac problems in surgical practice, cardiac emergencies, and the place of physiotherapy and of diet. Several of the author's colleagues who specialize in other fields have contributed chapters on the relation of allergy to the heart, the role of social service, and the various surgical measures now employed in the treatment of anginal pain, hypertension, effort syndrome, and suppurative pericarditis. There is an excellent section on electrocardiography, with more than 80 pages.

The author would probably be the first to insist that his book should be used as a supplement to other recognized texts, inasmuch as his chief interest is in treatment, whereas that of most "standard" texts is in diagnosis. But it is impossible to read this volume carefully without learning all the important diagnostic procedures and, in addition, far more about prognosis than is possible from books that do not include detailed case histories. The author's comments—wise, conservative, and lucidly stated—gain in cogency when made in connection with the diagnosis or treatment of a particular patient whose history and progress are recorded at some length. Even without case histories this would be an excellent volume for all practitioners who are entrusted with the care of cardiac patients, but the inclusion of such records adds greatly to its value. Some of these are necessarily brief, but many of them follow the course of patients for weeks, months, or even years, and display more clearly the variable responses to different therapeutic procedures than any other method could do. These do not follow any fixed pattern, but include the essentials; one of the most interesting and illuminating is presented in the form of a series of letters from a patient over a period of almost two years, with explanatory comments by the author.

Throughout the book one is impressed by the fact that Dr. Leaman writes of matters with which he has had long and intimate experience. His knowledge has obviously been derived not merely from careful reading of cardiovascular literature, or even from ward visits and the autopsy room, but also from the prolonged, day-to-day care of sick people in the hospital, office, and home. His discussions are marked by authority and wide knowledge of recent advances. The illustrations are superbly reproduced and add much to the value of the text. The author is to be congratulated upon having made a real contribution to the aspect of heart disease that seems to many of us the most important, but receives scant attention in most books.

H. M. Marvin.

Correspondence

To the Editor:

In his article on the duration of electrical systole in massive pericardial effusion (Am. Heart J. **22**: 35, 1941), Chen-Lang Tung states: "In the rather large literature of the electrocardiographic changes in pericardial effusion, no mention has been made as to the effect of such effusion on the Q-T duration." I wish to direct attention to the work of Dressler (*Klinische Elektrokardiografie,* 1937) and ter Horst (*Acta Med. Scand.* **101**: 362, 1939), both of whom described an abnormal *shortening* of the Q-T interval in pericardial effusion which they claimed could be used as a diagnostic aid. The latter investigator included a case wherein the decreased Q-T returned to normal after adequate pericardiocentesis, but close scrutiny of the protocol reveals that the limitation of systole was merely relative, not absolute.

From a personal study of four patients with pericardial effusion, I am able to confirm Tung's statement that the Q-T interval is not significantly shortened. Incidentally, in one of the two cases in which electrocardiograms were taken before and after tapping on several occasions, the Q-T interval varied significantly in only a single instance.

The value of Tung's thesis is limited, however, by the fact that the Q-T interval is not abnormally lengthened in all cases of cardiac failure.

Edward Shapiro, M.D.
Beverly Hills, Calif.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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